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ROUTINE TESTING FOR PORPHYRIA VARIEGATA

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It is now well established that a Mendelian dominant form of porphyria, which is not sex-linked and which may present with acute attacks or with a sensitive skin, is common among the White and Coloured populations of South Africa.[1-7] This form of porphyria, porphyria variegata, is a different disorder from intermittent acute porphyria[8] — the Mendelian dominant porphyria described by Waldenström in Sweden.[9,10] In other parts of the world both intermittent acute porphyria and porphyria variegata occur although they are comparatively uncommon. Among the Bantu population of South Africa symptomatic cutaneous porphyria, generally secondary to disturbed liver function, is frequently seen,[11] and it occasionally occurs among the White citizens of this country.

The high incidence of porphyria variegata among the White population of Southern Africa is shown by the fact that during the last 10 years I have personally attended 73 patients during attacks of acute porphyria and have detected 897 porphyrics in 118 porphyria-variegata families. In a screening experiment in 1957 two groups of White South Africans were screened for porphyria variegata using the methods described below.[12] Among 608 patients at a mental hospital 4 were found to have porphyria; and among 645 nurses, a special group with a high incidence of Afrikaners, 8, after full investigation, were found to have inherited the gene. Most attacks of acute porphyria follow the taking of barbiturates and particularly thiopentone anaesthetics. In 1958, 8 patients at the Provincial Hospital, Port Elizabeth, were known to have developed acute porphyria following thiopentone anaesthetics, and of these 3 died. A number of undiagnosed milder attacks of acute porphyria probably occurred. No patients with intermittent acute porphyria have been seen in Port Elizabeth.

Until we started routine testing for porphyria in Port Elizabeth there were usually one or two patients receiving treatment at the hospital for acute porphyria. As these patients generally required treatment in a private room with a special day and night nurse, the cost to the Administration must have been high, because they were often in hospital for some months and required a great deal of medical and nursing attention. The cost in suffering for the patients concerned and for their relatives was of much greater importance. Highly experienced physicians and surgeons frequently overlook the disorder and prescribe barbiturates or give a thiopentone anaesthetic to porphyrics.

It is by no means inevitable that patients who have inherited porphyria will develop acute porphyria after thiopentone. Some patients were given barbiturates or thiopentone on two or three occasions without a severe acute attack. In my own mind I liken the reaction to the firing of a gun: the pressure required to fire off an attack of acute porphyria varies from person to person and from time to time in the same person. For instance, acute porphyria is rare in children, and I have not seen a single case in a child under the age of 16; it is also uncommon after the age of 60. In males the incidence of acute porphyria is at its highest between the ages 17 and 60; and in women between the age of 17 and the menopause.

DIAGNOSING SOUTH AFRICAN GENETIC PORPHYRIA: PORPHYRIA VARIEGATA

In order to screen patients as a routine for porphyria variegata a very simple test is required. Patients are generally admitted to hospital the night before operation, and the test must be carried out before they are given thiopentone the following morning to exclude latent or quiescent porphyrics. In porphyria variegata there is nearly always, but not invariably, a high excretion of porphyrin in the stool during adult life, particularly during the period when the patient is most at risk. There is generally a slight increase in the stool porphyrin in children, but in many cases not enough to detect that they are porphyrics, unless a careful quantitative analysis is carried out. In old people the stool-porphyrin levels also drop. There is no simple single test for porphyria variegata that can be guaranteed to detect every case, because porphyria is a varying metabolic disorder. In many patients with quiescent porphyria there is a slight increase in the urinary porphyrin, but this also occurs in many conditions other than porphyria. On the other hand, an increased urinary porphyrin may not be found in porphyria if the urine is dilute. In my experience routine testing for increased porphyrin excretion in the stool is much more reliable than routine testing for increased urinary porphyrin. Furthermore, there are so many false-positive reactions in routine urinary testing that it is not possible to obtain the cooperation of a large group of doctors in using this test before operation.

In order to carry out the simple screening test that we use in Port Elizabeth, a small fragment of stool, such as can, if necessary, be obtained on a finger stall, is collected on a glass rod or wooden stick which is then inserted into a test tube containing 2 ml. of a solvent consisting of a mixture of equal parts of amyl alcohol, glacial acetic acid, and ether. The solvent is stirred until it has reached a light-brown colour and the liquid is then decanted into a clean test tube. The solution is then examined in ultraviolet light using a Wood's filter in a darkened room or a darkened box. In normal light the solution will look light brown in colour, whether or not it has come from a porphyric patient. In ultraviolet light the porphyric stool will show a brilliant pink fluorescence. This fluorescence is usually so strong that it persists even when the solvent is diluted several times. If the patient is not a porphyric the solution will be green or grey or perhaps just slightly orange when examined by a Wood's light. A quantity of chlorophyll in the stool also causes a pink fluorescence, because chlorophyll is a

porphyrin. The porphyrin of chlorophyll can be separated from copro- and protoporphyrin by adding 2 ml. of 1·5 normal hydrochloric acid to the solvent, shaking the mixture and allowing the acid solution to separate out to the bottom of the test tube. Copro- and protoporphyrin will pass into the acid solution at the bottom; chlorophyll porphyrin will remain in the ether solution at the top.

A high excretion of porphyrin in the stool does not necessarily mean that the patient is a porphyric, because a few other disorders can also cause a high stool porphyrin.[13] It has been found that some patients, who excrete increased porphyrin in the faeces but who are not porphyrics, have disorders in their alimentary tracts; 6 of these in the past year had cancer of the stomach or colon.

If a high excretion of porphyrin is found in the stool the patient should not be given barbiturates or sulphonamides until it is known whether or not the increased porphyrin is caused by porphyria. Further investigations must then be undertaken. The urine should be examined for excess porphyrin because usually, but not always, in porphyria variegata there is an excess of porphyrin in the concentrated urine as well as in the stool. The patient should be examined for a sensitive skin (on the back of the hands) and for a skin that abrades easily, and a careful history should be taken to ascertain whether any other members of the family, particularly on the male side, suffer from a sensitive skin. By correlating the personal and family history, the patient's symptoms and signs, and the presence or absence of porphyrin in the urine as well as in the stool, it is usually fairly easy to decide quite rapidly whether or not the patient is a porphyric. A patient born in Europe is unlikely to have porphyria variegata. It may be necessary in doubtful cases to repeat the examination of the stool on a few occasions, because in porphyria the porphyrin excretion continues, whereas in temporary disorders it is intermittent. I also make a practice of carrying out a barium meal and barium enema X-ray examination on patients who have a definite excess of porphyrin excretion in their stool, and whom I do not consider, from their personal and family history, to be porphyrics. This is done because some have been found to have cancer of the gastro-intestinal tract.

If an excessive amount of porphyrin is found in the stool and there is any doubt about the diagnosis, a quantitative analysis of porphyrin should be carried out. Fortunately in porphyria variegata the excretion of porphyrin is often 10 or 20 times the normal amount or even more. The upper limit of normal is arbitrary, but, if the coproporphyrin is above 30 μg. and the protoporphyrin is above 60μg., or the combined porphyrin above 75 μg./g. dry weight, the possibility of porphyria should be considered. In most adult patients with porphyria variegata the stool prophyrins are more than 200 μg./g. dry weight, and often more than 500 μg./g. dry weight. In this survey 20 specimens of stool from patients who had been found to have porphyria on routine testing were analysed quantitatively for stool porphyrin; the range was from 3,330 μg./g. dry weight to 164 μg./g. dry weight. The average was 1,339 μg./g. (686 μg./g. copro-, and 653 μg./g. protoporphyrin).

Increased porphyrin excretion in the urine can occur in many other conditions besides porphyria, in particular in lead poisoning and in disordered liver function; examination of the urine does not, therefore, provide such a useful screening test for South African genetic porphyria in the quiescent phase as screening the stool. It is, however, a very useful confirmatory test. A simple way of examining the urine for excess porphyrin is to use the solvent mentioned above. One ml. of the solvent is added to 10 ml. of urine; the mixture is well shaken and then left to stand for a few minutes so that the solvent floats to the top.[14] The liquid is then examined in Wood's light and, if an excess of porphyrin is present, the ether solution at the top of the test tube will show a red fluorescence. The urine should also be examined spectroscopically, but considerable practice in the use of the spectroscope is necessary before the small increase in porphyrin excretion often found in the urine in quiescent porphyria can be detected.

In Swedish porphyria, or intermittent acute porphyria, porphobilinogen and delta-aminolaevulic acid are usually found in the urine during the quiescent phase.[10] However, in porphyria variegata there is no increase in the porphobilinogen in the quiescent phase, but it is present during an acute attack. This fact can be used to differentiate acute from quiescent porphyria variegata. In acute porphyria variegata the Watson-Schwartz test for porphobilinogen is strongly positive.[15] This test is carried out by adding 2 ml. of Ehrlich's aldehyde reagent to 2 ml. of urine and shaking the mixture. Two ml. of a saturated solution of sodium acetate is then added and, if either porphobilinogen or urobilinogen is present, a purple colour results. The urobilinogen is soluble in chloroform and, therefore, if chloroform is added to the mixture and it is shaken again and allowed to separate, urobilinogen will come down in the chloroform layer, but porphobilinogen will stay in the aqueous solution. If acute porphyria is suspected in porphyria variegata, the Watson-Schwartz test with Ehrlich's aldehyde will quickly show whether or not the patient has an acute attack. This test, it must always be remembered, cannot be used for detecting quiescent porphyria variegata, because in the quiescent phase this test is negative.

ROUTINE TESTING IN PORT ELIZABETH

At a hospital committee meeting at the Provincial Hospital in Port Elizabeth in 1959 my proposal was accepted by the Medical Superintendent, Dr. J. H. McLean, and the committee, that all patients who were admitted to hospital should have their stools tested as a routine for porphyrins before a thiopentone anaesthetic is given or barbiturates administered. The Provincial Hospital in Port Elizabeth is an open hospital attended by about 160 doctors, and only a very high degree of cooperation among these doctors, and especially among the anaesthetists, made this routine testing possible. Normally a specimen of stool was sent to the South African Institute for Medical Research* the day before the operation. If necessary, the stool was obtained by an enema or by a gloved finger. In emergencies the patient was sent direct to the theatre and the anaesthetist carried out the routine test in the anteroom of the theatre. A screening lamp was kept in the main theatres and at the maternity block in the hospital. Routine testing was also instituted at St. Joseph's Hospital, a

* The Port Elizabeth branch.

private nursing home, where the sisters tested the specimens. Records were kept and I was informed about every positive stool or about every 'query positive' result. In these cases I investigated the faeces and urine and the patient personally. During the first 2 months there was an excessive number of false positives due to extreme zeal on the part of the laboratory technicians who carried out the tests and who reported every specimen which showed a slight orange colour. With increasing experience the number of false positives became small. There were, however, probably as many patients who excreted slightly increased porphyrin without being porphyrics, as there were those who were found to have porphyria on thorough investigation.

Between 1 April 1959 and 31 March 1960, 23 patients were found to have porphyria at the Provincial Hospital and 5,647 tests were carried out on adults (1,929 male and 3,718 female). A number of these patients belonged to known porphyric families, and a few of the patients were known porphyrics who had been diagnosed previously. If a patient had not been investigated previously and was discovered on routine testing, a specimen of stool was sent to Dr. H. D. Barnes, of the South African Institute for Medical Research, Johannesburg, for a quantitative analysis of the stool porphyrin. He carried out a quantitative analysis of stool on 20 of the porphyrics. Most porphyrics whose porphyrin was analysed had a very high stool porphyrin, but, as can be seen from Table I, 2 of the older patients (Nos. 17 and 19) did not have a greatly increased stool porphyrin and, in fact, No. 19 was missed by the technician who did the routine tests. Nevertheless, few patients with porphyria could have been missed among those who were tested, because, unlike in previous years, we did not have unexpected attacks of acute porphyria.

At St. Joseph's Hospital 6 patients with porphyria were admitted during the 12-month period and 811 routine tests were carried out. During the early days of routine testing a young man, No. 24, was admitted to the hospital complaining of severe abdominal pain, vomiting, and constipation. Two enemas gave no result and the stool was not tested for porphyria as a routine. Unfortunately the urine was not tested either and the surgeon, who knew porphyria well and who had diagnosed a number of patients with porphyria in the past, nevertheless suspected that this patient had intestinal obstruction. The patient was given 0·35g. of thiopentone so that a laparotomy could be performed. At operation no definite pathology was found, but it was thought a condition of partial obstruction was present, and a caecostomy was carried out. Two days later the sisters noticed that the urine was dark-red in colour and, as soon as it was examined, it was found to contain a great excess of porphyrin and the Watson-Schwartz test was strongly positive. The patient became delirious and had to be fed intravenously. He was given intravenous saline, calcium by injection, potassium, etc. He developed a number of epileptic attacks and also tetany. When the anaesthetist, who had given him the thiopentone, visited the ward to see another patient, the patient with acute porphyria attacked him with a water bottle and injured his head. (The patient was delirious and had not recognized the anaesthetist, but thought he was a burglar.) Unfortunately this patient become paralysed and died from acute cardiac collapse. At autopsy a very high level of porphyrin was found in his bile and in his liver. On investigation two members of his immediate family were found to have porphyria. This unfortunate catastrophe encouraged the anaesthetists to make certain that their patients were given a routine test before the administration of thiopentone.

The details about the 29 patients who were found to have porphyria during the 12 months are described in Table I. Certain patients require special mention:

Case 1, No. 3

This patient had 2 previous laparotomies with thiopentone anaesthetic and the surgeon remembered that he had a very stormy convalescence — he became very agitated and ruptured the wound. On this occasion he was admitted for a repair of his post-operation abdominal hernia. Porphyria was detected by routine testing, and he was given a gas, oxygen and ether anaesthetic. He had no ill effects after the operation. The surgeon commented that his excellent convalescence was quite unlike the previous occasions.

Case 2, No. 5

This patient was also admitted for repair of his hernia after a previous operation when he had thiopentone. On the previous occasion the abdominal repair ruptured and had to be re-sutured. Unfortunately, although the anaesthetist knew that the patient had porphyria, he was not convinced of the danger and he gave him 0·3 g. of thiopentone. One week later the patient developed severe abdominal pain, vomited repeatedly and was clearly very ill. The Watson-Schwartz test by then was positive. He ruptured his wound.

Case 3, No. 7

This patient was admitted from the country with the diagnosis of acute porphyria after taking nembutal. She made a good recovery.

Case 4, No. 12

This patient belonged to a large porphyric group that had been previously investigated. She had not been tested for porphyria before admission, but she had been warned about the danger; nevertheless, she did not inform her doctor that she belonged to a porphyric family. On routine testing she was found to have porphyria and was given no barbiturates.

Case 5, No. 16

This patient developed a mild attack of acute porphyria after taking seconal tablets for a few nights. A previous stool test had been reported negative, but when I saw her the stool test was positive. She had a mild attack of acute porphyria, but she made a good recovery.

Case 6, No. 19

This 60-year-old patient was admitted to hospital for a hysterectomy. I had attended her daughter for cutaneous porphyria in the past and had also investigated the family. Nine members of her family had porphyria. This patient refused investigation because she would not admit that she had inherited any genes from an Afrikaner ancestor. She was convinced that she was of pure 1820 British settler stock. Her stool test was negative, and she was given thiopentone and made a good recovery. A quantitative analysis of her stool some weeks after the operation showed, however, that there was some increase in the stool porphyrin. Ten years ago she became acutely ill a few days after a cholecystectomy; she was emotionally disturbed and passed dark urine. It took her 3 months in hospital to recover.

Case 7, No. 28

This patient was admitted for laparotomy because he was deeply jaundiced. His stool was clay-coloured and his urine contained a great excess of bile. He belonged to a known porphyric family and previously he had had a great excess of porphyrin in his stool. His son is also a porphyric. He had an obstruction to his bile duct from a neoplasm of the pancreas, and neither bile nor porphyrin was escaping into his intestinal tract. His urine contained increased porphyrin. It must be remembered that if there is obstruction

TABLE I. PATIENTS FOUND TO HAVE PORPHYRIA VARIEGATA ON ROUTINE SCREENING, APRIL 1959 - MARCH 1960
PROVINCIAL HOSPITAL, PORT ELIZABETH, ROUTINE TESTS: 5,647 (1,929 MALES, 3,718 FEMALES)

No.	Sex	Age	Initial	Diagnosis on admission	Screening faeces	Screening urine	Watson-Schwartz test	Skin sensitive	Treatment instituted	If routine stool test	Analysis/porphyrin stool dry weight		Porphyrics found in family	Outcome
											Copro µg.%	Proto µg.%		
1	F	27	B	Abdominal pain, insomnia, on seconal for sleep	++++	+++	++	+−	Acute porphyria diagnosed, conservative treatment	Yes	750	720	3	Recovered
2	F	31	S	Menorrhagia—for D & C, porphyria diagnosed 1958	++++	+	−	−	Gas, oxygen, no pentothal	Yes but known porphyric	−	−	−	Recovered
3	M	45	D	Had 2 previous laparotomies with pentothal, now admitted for repair abdominal hernia	++++	+++	−	++	Gas, oxygen, ether. No ill effects after operation	Yes	294	494	3	Recovered
4	F	35	W	For colporrhaphy	++++	−	−	−	Gas, oxygen, ether. No ill effects after operation	Yes	595	870	2	Recovered
5	M	32	C	For hernia repair after previous operation, when he had pentothal. On previous occasion abdominal repair ruptured and had to be resutured	++++	+	−	++	Although anaesthetist knew he had porphyria, 0·3 g. of pentothal was given. One week later abdominal pain and vomiting. Watson-Schwartz test positive. Ruptured wound	Yes	395	610	3	Recovered
6	F	25	deK	In labour. Had acute porphyria June 1958 after seconal	++++	+	−	−	No barbiturates given	Known porphyric	−	−	4	Recovered
7	F	33	E	Admitted as acute porphyria after nembutal	++++	+++	+++	−	Intravenous glucose, saline, calcium, and potassium	Acute porphyria	−	−	3	Recovered
8	F	39	deR	Admitted for hysterectomy	++++	−	−	−	Gas, oxygen, ether. No pentothal	Yes	750	850	3	Recovered
9	F	36	M	Admitted for hysterectomy	++++	+	−	+	Gas, oxygen, ether. No pentothal	Yes	486	794	6	Recovered
10	F	31	P	In labour	++++	+	−	+	No barbiturates given	Yes	1,210	1,260	1	Recovered
11	M	42	P	After a few days of seconal had acute abdominal pain and vomiting; admitted for laparotomy	++++	++	+++	+	Treated conservatively; salt, calcium, etc.	Yes	1,195	860	−	Recovered
12	F	27	W	Hypertension during pregnancy	++++	+	−	−	Conservative. Although not previously tested, a member of a porphyric group already investigated. Her father and cousin died a few years ago of acute porphyria at this hospital. She had been warned about porphyria but did no tell her doctor	Yes	510	600	33	Recovered
13	F	45	N	Admitted as severe cutaneous porphyria	++++	+++	−	+++	Conservative	Known porphyric	−	−	3	Recovered
14	F	27	E	Cutaneous porphyria suspected by dermatologist	++++	+++	−	+++	Conservative	Suspected porphyria	−	−	4	Recovered
15	F	79	E	Known porphyric. Admitted for operation—lipoma on leg	+++	+	−	−	Gas, oxygen, ether	Yes. Known porphyric	−	−	11	Recovered
16	F	49	M	Acute porphyria after seconal. A previous stool test had been reported negative	+++	+++	+++	−	Glucose, saline drip, calcium gluconate, potassium chloride, etc.	Yes	200	206	2	Recovered

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PROVINCIAL HOSPITAL, PORT ELIZABETH, ROUTINE TESTS: 5,647 (1,929 MALES, 3,718 FEMALES) (Cont'd.)

16	F	49	M	Acute porphyria after seconal. A previous stool test had been reported negative	+++	+++	+++	–	Glucose, saline drip, calcium gluconate, potassium chloride, etc.	Yes	200	206	2	Recovered

TABLE I. PATIENTS FOUND TO HAVE PORPHYRIA VARIEGATA ON ROUTINE SCREENING, APRIL 1959 - MARCH 1960
PROVINCIAL HOSPITAL, PORT ELIZABETH, ROUTINE TESTS: 5,647 (1,929 MALES, 3,718 FEMALES) (Cont'd.)

No.	*Sex*	*Age*	*Initial*	*Diagnosis on admission*	*Screening faeces*	*Screening urine*	*Watson-Schwartz test*	*Skin sensitive*	*Treatment instituted*	*If routine stool test*	*Analysis/porphyrin stool dry weight*		*Porphyrics found in family*	*Outcome*
											*Copro µg.% *	*Proto µg.%*		
17	M	55	F	Admitted for correction of squint	+	++	–	+	Conservative	Yes. Repeated after 3 months	96 102	97 119	1	Recovered
18	M	26	M	Admitted for reduction of dislocated shoulder	+++	+	–	–	Gas, oxygen, ether	Yes. Known porphyric	–	–	16	Recovered
19	F	60	F	Admitted for hysterectomy	–	+	–	–	As stool test was 'negative' given 0·35 g. of pentothal for hysterectomy. Made good recovery.	Yes	72	92	9	Recovered
			Sister	Known porphyric, retested	+++	++	–	+	Her daughter and sister were known porphyrics. She had formerly refused to send a specimen for testing. Ten years previously she collapsed 10 days after cholecystectomy and took 10 weeks to recover					
			Daughter	Known porphyric with a very sensitive skin, retested	++++	+++	–	+++						
20	M	53	C	Admitted as ?coronary thrombosis	++++	Trace	–	++	Conservative. Although not previously tested, a member of a porphyric group already investigated	Yes	395	343	29	Recovered
21	F	19	N	Abdominal pain during pregnancy	++++	–	–	+++	Conservative	Yes	372	645	1	Recovered
22	F	48	K	Admitted for treatment severe backache	++++	++	–	+++	Back manipulated under gas and oxygen anaesthetic	Yes. House doctor diagnosed porphyria	1,000	875		Recovered
23	F	58	B	Carcinoma of cervix	++++	++	–	+	Gas, oxygen, ether. This patient was found to belong to a large clan of porphyrics from the Ladismith area	Yes	1,010	870	29	Recovered from operation
				ST. JOSEPH'S HOSPITAL, PORT ELIZABETH, ROUTINE TESTS 811 (257 MALES, 554 FEMALES)										
24	M	27	R	Took sonergan (butobarbitone) 2 at night for 5 days. Developed severe abdominal pain, vomiting and constipation. Two enemas, no result; so stool not routine tested for porphyrin. Urine not tested. Given 0·35 g. of pentothal. Laparotomy and caecostomy. Acute porphyria recognized 2 days later	++++	++++	+++	+–	Delirious, attacked and injured anaesthetist a few days later. Fed intravenously. Saline, calcium, potassium, etc. Had convulsions, tetany. Became partly paralysed; knee jerks absent. Died sudden cardiac collapse	Routine test missed	1,220	615	2	Died
25	F	41	M	Admitted for removal of ovary. Was to have pentothal anaesthetic	++++	++	–	+	Gas, oxygen, ether	Yes	875	590	–	Recovered
26	F	47	N	Admitted for hysterectomy (fibroids)	++++	+	–	–	Gas, oxygen, ether	Yes. Known porphyric	–	–	11	Recovered
27	F	31	L	Admitted for hysterectomy (fibroids)	++++	–	–	+	Gas, oxygen, ether. Had pentothal for previous operation 6 years previously. Good recovery, but skin of hands abraded easily since	Yes	2,060	1,270		Recovered
28	M	62	L	Admitted for laparotomy. Deeply jaundiced	– Clay colour	+ Bile ++	–	–	Gas, oxygen, ether. Neoplasm of pancreas found. Cholecystenterostomy	Yes. Known porphyric	very low		31	Recovered from operation
29	F	14	vR	Admitted for tonsillectomy	+++	–	–	–	Mother had acute porphyria after pentothal 1952. Recovered	Yes	250	395	31	Recovered

to the bile the stool test for porphyrin will inevitably be negative.

THE INCIDENCE OF PORPHYRIA VARIEGATA IN THE EASTERN CAPE

During the 12-month period 23 porphyrics were found at the Provincial Hospital out of 5,647 cases on routine testing in adults (17 female and 6 male). Children were not tested. More women are admitted than men, and this no doubt accounts for the higher incidence amongst the women. The fact that more women are given barbiturates and have operations is, in my opinion, the chief reason for the higher incidence of acute porphyria in women. Fifty-three further undiagnosed cases of porphyrics were found on investigating the families. During the 12-month period about 10,900 adult patients were admitted to the two hospitals, excluding readmissions, and 60% of these were tested for porphyria. Many of the older patients, who were not admitted for operation and not given barbiturates, were not tested. No doubt a number of these patients also carried the gene for porphyria. During the present year we are endeavouring to test all admissions to hospital. A stamp has been placed on the outside of the hospital folders marked 'porphyria positive' or 'porphyria negative' and, as the patients are tested, the result of the test is clearly marked on the folder. At St. Joseph's Hospital 811 routine tests were carried out and 6 patients were found to have porphyria. At both hospitals the only patient who died was one whose routine test had been missed. At the Provincial Hospital the incidence of porphyria was 1 out of 246 routine tests. Taking the two hospitals together the incidence was 1 out of 223 routine tests. In round figures the incidence of porphyria variegata among hospital admissions in Port Elizabeth appears to be at least 1 in 250. The hospital admissions represent a good cross-section of the community, but have a higher incidence of porphyria than the healthy population, since some patients are admitted to hospital because of their porphyria. Nevertheless, from the number of porphyrics I have detected and the number of healthy porphyrics admitted to hospital, I estimate the incidence of porphyria variegata among the White population of the Eastern Cape to be about 1 in 350.

The incidence of porphyria variegata can be estimated by the following indirect method: Patients with porphyria variegata in South Africa can be traced back to one original family, that of Gerrit Jansz (van Deventer) who married Ariaantje Adriansse at the Cape in 1688.[16] Gerrit had 8 children and porphyric families can be traced back to 4 of them. The first daughter, Jacomintje, married the first van Rooyen to come to South Africa, Cornelis, who came from Gorkum in 1713. Four of Cornelis van Rooyen's 11 children were sons who carried on the family name. Porphyric groups can be traced back to 5 of the 11 children, who, therefore, inherited the gene for porphyria from Jacomintje. Another daughter of Gerrit Jansz married one of the first Nels. Yet another daughter married twice and had porphyric descendents by both marriages. She first married Phillipus Snyman, and then Jan Hendrik Debes. The fourth porphyric child of Gerrit was a son and he had 12 children — the van Deventer family. At least 10 of the grandchildren of the first porphyric in South Africa appear to have carried the gene for porphyria.

Prof. S. Pauw[16] has shown that one million of the White population of South Africa hold 40 original family names and are descendants of 40 original burghers and their wives. The males among them inherit their Y-chromosomes from 40 original free burghers. For instance, except for illegitimacy and an occasional recent immigrant, the male van Rooyens inherit their Y-chromosomes from Cornelis van Rooyen. Male sex is inherited according to the same Mendelian dominant law as porphyria, i.e. on an average about half the children inherit the Y-chromosome and male sex. Therefore, the incidence of the name van Rooyen in a community should run roughly parallel to the incidence of porphyria. In the past, porphyric families were just as large as the other families in South Africa and it is only recently, since the introduction of barbiturates, that the gene for porphyria has become a potentially lethal gene. The names of 6 common porphyric families in the Eastern Cape are van Rooyen, Barnard, Potgieter, van Niekerk, Nel and Ferreira. These are not the commonest names. Table II shows the number of patients with these

TABLE II. A SUGGESTED METHOD OF OBTAINING A ROUGH GUIDE OF THE INCIDENCE OF PORPHYRIA VARIEGATA IN A HOSPITAL OR COMMUNITY IN SOUTHERN AFRICA—WITH EXAMPLES (ADULTS ONLY)

	Two Port Elizabeth hospitals, April 1959 - March 1960		Hospital admissions, 1959, excluding readmissions in same year				
Name	*Patients tested*	*Patients admitted*	*Pretoria General*	*Karl Bremer*	*Groote Schuur*	*Johannesburg General*	*Addington*
van Rooyen	43	66	85	16	13	38	26
Barnard	50	91	72	20	15	30	10
van Niekerk	28	44	101	31	27	80	26
Potgieter	43	62	111	10	6	45	13
Nel	55	91	131	38	28	91	13
Ferreira	60	80	47	11	4	26	12
Average of names	46·7	73·7	91·7	21·0	16·5	51·7	16·7
¾ of van Rooyens	32	49	64	12	10	29	20
¾ of average of all 6 names	35	55	68	15	12	39	13
Totals, excluding readmissions	6,458	10,900	23,082	4,678	7,490	17,433	12,287
Porphyrics detected	29						
Approximate incidence estimated	1/250	1/250	1/400	1/400	1/750	1/600	1/1,000

names who were given routine tests at the Provincial Hospital, Port Elizabeth and St. Joseph's Hospital, and the total number of admissions with these family names at these two hospitals, excluding readmissions.

The number of porphyrics in a large South African community should on an average be at least equal to the number of male van Rooyens, who can themselves be averaged by taking half the total van Rooyens in a group. In fact the first van Rooyen married one of the 4 porphyric children of Gerrit Jansz; however, she was the eldest, and 5 of the 10 known porphyric grandchildren of Gerrit Jansz belong to this family. In my experience about two-thirds of all South African porphyrics can be traced back to the van Rooyen clan, although most of them do not hold the van Rooyen name today. Therefore I suggest the number of porphyrics in a South African community can be roughly estimated by taking three quarters (a half plus a quarter) of all the van Rooyens, male and female. This estimate can be checked by averaging the 6 common names mentioned above and multiplying by three quarters. Table II shows a rough estimate of the expected number of porphyrics at Port Elizabeth hospitals and other large South African hospitals using these two methods.

By analogy other hospitals in Southern Africa can make a rough estimate of the number of porphyrics admitted during the previous 12-month period by adding up the van Rooyens who have been admitted in that period and multiplying by three quarters, checked, in case the name van Rooyen is disproportionately common, by averaging the 6 names mentioned above and multiplying by three quarters.

It is early to estimate the total number who have inherited the gene for porphyria variegata from Gerrit or his wife Ariaantje. Port Elizabeth is known as the 'City of the 1820 settlers' and yet in this predominantly English-speaking city the incidence of porphyria appears to be about 1 in 250. Porphyria is common among the descendants of trekboer families, i.e. boer families that trekked eastwards to the Eastern Cape and went on the Great Trek to the Transvaal and Natal. It seems probable that the incidence of porphyria is lower in Johannesburg, Durban and Cape Town where there have been a large number of more recent immigrants, and this is confirmed by the estimations made in Table II. Nevertheless, there are 15,000 van Rooyens in the country of whom half have inherited their Y-chromosomes from Cornelis van Rooyen, and Cornelis' wife was only one of Gerrit's 4 porphyric children. If I were to make an estimate, which will be confirmed or refuted by posterity, of the number of persons who have inherited the gene for porphyria variegata amongst our South African community, including the Rhodesias, I would say it is 8,000 $\pm$ 2,000, bearing in mind the fact that a number of porphyrics have inadvertently lost their lives through acute porphyria during the last 50 years. As far as is known they all inherited the gene from one ancestor who married at the Cape in 1688.

SUMMARY

It has been well established that the gene for porphyria variegata is very common among the White and Coloured populations of Southern Africa. These porphyric families descend from one original couple who married at the Cape in 1688.

If porphyrics are given barbiturates, and in particular a thiopentone anaesthetic, an attack of porphyria, which is highly dangerous to life, may be inadvertently precipitated. Porphyria variegata in the quiescent phase is not easily detected unless the diagnosis is suspected or a routine test of the stool is carried out. Therefore, in Port Elizabeth the routine testing of all admissions to hospital for porphyria variegata, before the administration of thiopentone and other barbiturates, was introduced. During the first 12-month period 29 porphyrics were found among the hospital admissions and 6,458 routine tests were carried out. It is estimated that the incidence of this gene among the hospital admissions is about 1 in 250 in the Eastern Cape and it is considered that this reflects the incidence of porphyria amongst the White population of the Eastern Cape.

A method is described for making a rough estimate of the expected number of persons with porphyria variegata in any large community or hospital in Southern Africa.

It is strongly recommended that routine testing be instituted in all hospitals in Southern Africa before the administration of barbiturates and especially before the administration of thiopentone anaesthetics. As porphyria variegata is generally easily detected by routine testing, the doctor in South Africa leaves himself open to criticism if a patient develops acute porphyria after the administration of thiopentone — if the test has not been done.

It is estimated that the total number of people who have inherited this gene in Southern Africa is about 10,000.

The institution of routine testing for porphyria variegata at the Provincial Hospital, Port Elizabeth and at St. Joseph's Hospital was made possible by the unstinting cooperation of Dr. J. H. McLean, Superintendent of the Provincial Hospital, and the hospital committee; the Reverend Mother and Sisters of St. Joseph's Hospital, and all the doctors who use the hospitals. I should particularly like to thank the anaesthetists who insisted on routine tests before the administration of thiopentone anaesthetics. I should like to thank the Director of the South African Institute for Medical Research, Johannesburg, who authorized the Institute in Port Elizabeth to carry out the routine tests free of charge for 1 year; Dr. W. C. Harington who provided facilities; and Mr. Welsh and his assistants who did the tests. Mrs. Basford and Mrs. Mitchell did the secretarial work. I should also like to thank Dr. H. D. Barnes, of the SAIMR, Johannesburg, for carrying out the quantitative analysis of stool porphyrin on 20 patients who were not known to have porphyria before the routine tests. I am indebted to the Medical Superintendents of the Groote Schuur, Johannesburg General, Pretoria General, Karl Bremer, and Addington Hospitals for providing statistical information for Table II. The South African Council for Scientific and Industrial Research made a grant in aid of the administrative expenses.

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VAN DIE REDAKSIE : EDITORIAL

MEDIESE PROBLEME VAN DIE ADOLESSENT

Uit die volksgebruike van die meeste gemeenskappe, of hulle nou ook al primitief of beskaafd is, is dit duidelik dat die rypingsjare van jeugdiges as 'n baie belangrike fase in hul lewens beskou word. Hierdie opvatting berus op die algemene ervaring dat adolessente persone wel *anders* is en dat hulle nie behandel kan word soos klein kindertjies of volwassenes nie.

Ongelukkig slaag die samelewing nie altyd daarin om die jeugdige se onrustige gemoedslewe goed te verstaan nie, met die gevolg dat daar 'n reaksie van afkeuring aan die kant van die samelewing, en 'n reaksie van verset aan die kant van die jeugdiges ontstaan. Hierdie toestand van sake openbaar hom dan byvoorbeeld in die ontstaan van eendstert-bendes en ander weerspannige groepe.

Ons leef egter in 'n tyd van ongekende spanning en drukte op alle terreine van die lewe — 'n toestand van sake wat nie net op politieke gebied tot uiting kom nie, maar ook op nagenoeg alle gebiede van die maatskaplike lewe. Oor die algemeen gesproke het ons byvoorbeeld, soos die meeste ander Westerse nasies, 'n bevolking van stadsbewoners geword — selfs grotendeels 'n bevolking van kamer- en woonstelbewoners. Daarby het die moderne verkeersmiddels, en inligtingsdienste soos die pers en die radio, bygedra tot 'n verbrokkeling van gevestigde gebruike en waardes, sodat daar 'n geslag van jeugdiges ontstaan het wat nie die verankering het wat hul ouers gehad het nie. Die emansipasie van die jeug het gouer 'n groter finaliteit bereik as ooit tevore.

In die lig van die feite wat ons hier kortliks opgenoem het, is dit dus meer dringend nodig as in die verlede dat die gemeenskap sy jeugdiges — wat sy volwassenes van môre is — goed sal verstaan. Die meeste moeilikheid wat daar in die wêreld is, ontstaan reeds as gevolg van gebrekkige individuele reaksies van persone en van nasies teenoor mekaar. As 'n gemeenskap kan ons dit dus nie bekostig om die bande met ons jeugdiges verder te sien verbrokkel nie.

Dit is interessant en ontstellend om te sien in hoe 'n mate ons, selfs in hierdie wetenskaplike eeu, in gebreke gebly het om aan ons jeugdiges dieselfde nougesette aandag en sorg te gee as wat ons byvoorbeeld gedoen het ten opsigte van klein kindertjies en oumense. Die kindergeneeskunde en die geriatrie het ontwikkel as twee hoogs gespesialiseerde vertakkinge van die geneeskunde. En in die samelewing self is daar 'n wydverspreide besef van die spesiale en eiesoortige behoeftes van suigelinge en oumense. Maar, die betekenis en die implikasies van die rustelose en woelende gemoedslewe van die jeugdige word nog te dikwels totaal misken.

Dit is dus goed om te weet dat daar persone en inrigtings is wat dit vir hulle ten doel gestel het om 'n spesiale studie van die adolessent te maak. Twee boeke wat onlangs verskyn het en wat handel oor mediese en algemene probleme van adolessente persone, verdien spesiale vermelding. Die eerste is 'n handboek oor *Medical Care of the Adolescent*[1] wat geskryf is deur Dr. J. K. Gallagher, hoof van die Afdeling vir Adolessente van die Children's Hospital Medical Centre, Boston. Hierdie waardevolle bydrae tot ons kennis van die adolessent en sy mediese probleme handel oor 'n wye verskeidenheid van onderwerpe, soos byvoorbeeld die persoonlikheidstrekke en emosionele behoeftes van die jeugdige, hoe hy of sy benader en ondersoek moet word, en spesiale toestande waaraan jeugdiges dikwels onderhewig is, byvoorbeeld skolastiese vertraging, sportbeserings, groeiprobleme, gedragsmoeilikhede, geslagsprobleme, epilepsie, hartsiekte, dismenoree, ens. Daar word deurgaans 'n poging aangewend om aan te toon hoe die veranderende fisiologie en die ontluikende persoonlikheid van die adolessent in aanmerking geneem moet word by oorwegings oor hoe hy versorg en behandel moet word.

Die ander bock waarna ons verwys het is geskryf deur Dr. J. Hemming[2] en dit handel meer spesifiek oor die probleme van adolessente dogters. Die skrywer probeer om die faktore te ontleed wat daartoe sal bydra dat dogters gewillig sal wees om die hulp en leiding wat hulle wel nodig het, te aanvaar. Sy aanbevelings verdien die ernstige aandag van almal wat graag daartoe sou wou bydra om 'n gelukkiger, gesonder, en meer emosioneel-volwasse geslag van mense voort te bring.

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SCREENING FOR PORPHYRIA

Porphyria variegata, which is particularly common in South Africa, is inherited as a Mendelian dominant trait. Until the era of sulphonamides and barbiturates its importance was more academic than practical. We know now, however, that there is a possibility of serious, even fatal, attacks of acute porphyria being precipitated by these drugs in patients suffering from porphyria variegata. Even if an acute attack is not brought about, the resistance of these patients to future acute attacks may be lowered.

In this issue of the *Journal* Dr. G. Dean highlights the problem in his report of the routine screening of patients admitted during one year to the Provincial Hospital and the St. Joseph's Hospital in Port Elizabeth. From 1 April 1959 to 31 March 1960, 6,458 routine tests were carried out at the two institutions, and twenty-nine patients were found to have porphyria variegata. Dean points out that this variety of porphyria is difficult to detect in its quiescent phase unless routine stool and urine tests are carried out. Among the families of the twenty-nine patients a further fifty-three hitherto undiagnosed porphyria cases were discovered. There was only one death after thiopentone anaesthesia among all admissions to the two institutions during the year under review. The patient who died was a porphyric who presented with apparent intestinal obstruction and whose stool could not be obtained for examination. His urine was not

examined either and, after a stormy postoperative period, he died. From his figures Dean considers that about 1 in 250 of the hospital admissions in the Eastern Cape have the gene for porphyria variegata, but this is probably slightly higher than the incidence outside the hospital.

The facts presented by this routine testing are important and disturbing. Dean believes that throughout Southern Africa there are approximately 8,000 White and Coloured porphyrics among the descendants of the original Dutch settlers, Gerrit Jansz and his wife Ariaantje, from one of whom the gene was inherited. From estimates he has made of hospital admissions at other large centres in the Union, it seems that there may be a higher proportion of these descendants in the Eastern Cape, but that the incidence of porphyrics will be found to vary from about 1 in 400 at the General Hospital, Pretoria, to 1 in 1,000 at the Addington Hospital, Durban.

The only centre where routine testing has so far been carried out is Port Elizabeth. However, with the extremely common use of barbiturate anaesthetics, not to mention other barbiturates and the sulphonamides, it is reasonable to suggest that this screening should be undertaken in other parts of the Union. It will then be possible to tell whether Dean's figures, and the important assumptions he draws from them, can be substantiated elsewhere. If his estimates are proved correct, an important contribution to preventive medicine throughout South Africa will have been made.

PERSONAL DATA TO BE CARRIED IN CASE OF EMERGENCY

In 1958 we commented[1] on the difficulty facing casualty departments and private doctors when patients with open wounds require tetanus prophylaxis. Although immunization with tetanus toxoid is becoming more common, the patients themselves seldom know whether they have been immunized, or, even if they know this, they may be unconscious after an accident. Yet they need protection against possible tetanus and have perforce to be given antitetanus serum with its concurrent dangers. It was suggested then that their immunization history should be carried on the person in some acceptable form.

In this issue of the *Journal* we publish two letters dealing with other aspects of the same problem — one from a doctor, the Medical Superintendent of the McCord Zulu Hospital, Durban, and the other from a non-medical man, the former chairman of ESCOM.

There is an obvious and urgent need for some form of identification of people who are sensitive to various drugs or who suffer from a variety of illnesses which may render them unconscious in circumstances where a medical history is not available. Many conditions where this identification might be lifesaving spring to mind. These include: sensitivity to penicillin and ATS, diabetics taking insulin, porphyrics who may not be given sulphonamides or barbiturates,* bleeders who may need emergency operations, and so on. In this regard, with iatrogenic diseases and sudden catastrophes occurring more and more often after the use of some modern drugs, it is our duty to make every attempt to safeguard our patients, wherever possible, from these dangers. Doctors, too, would be prevented from innocent errors of commission if these facts were available.

What would be the best way to provide the identification in these cases? Where would the list end? These problems require careful thought and discussion. One of our correspondents suggests that suitable internationally-acceptable symbols should be decided on, and then tattooed on the skin. This would obviously be the most permanent way of recording the information, and it would certainly always be with the patient, but it is doubtful if this method would be aesthetically acceptable to many people.

Whatever method is eventually used, the whole problem must be tackled sooner or later. Ways and means of overcoming the difficulties will have to be found, and members of the medical profession should take the initiative in this matter.

* See Editorial article on 'Screening for porphyria' and Dr. G. Dean's article on 'Routine testing for porphyria variegata' on pages 752 and 745 of this issue of the *Journal*.

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MELANOGENESIS: THE MECHANISM OF SKIN PIGMENTATION

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The colour of a man's skin always arouses interest; you notice it at once and immediately draw conclusions, often false, which place him in some ethnic group. Blemishes, brought about either by excessive, patchy pigmentation or by its opposite, causing large decolourized blotches, give rise to great concern and mental distress. Of recent years the racial distribution pattern of skin colouring has given rise to special legislation. And sporadic social upheavals can be traced to the prejudice inherent in our attitude towards this dermatological characteristic.

Fortunately, however, the concern of this article is only with the biochemical processes in the epidermis which result in pigmentation, as well as with the disturbances which may arise in the normal functioning of these processes. The whole elaborate performance is admirably described and considered from every angle by various writers in a special number of the *Journal of Investigative Dermatology*[1] reporting the proceedings of a symposium held at Brook Lodge, Michigan, USA, in March 1958. The writer freely acknowledges his indebtedness to this fertile source of information in presenting this condensed account.

The burden of performing the intricate physicochemical operations for the production of skin pigment is borne by a highly specialized epidermal cell, the *melanocyte*. Its function is to make and distribute that special substance,

melanin, which gives the dark tint to the skin in coloured races and which constitutes the carefully cultivated, cosmetically acceptable, tan in fair-skinned individuals. This it achieves in response to various stimuli and inherited trends under the curbing and guiding influence of other physiological processes.

Ordinarily, sunlight supplies the necessary energy for initiating the pigmentation process when this is required. The ultra-violet light (UVL) division of the solar spectrum, itself a mere fraction of the vast electro-magnetic spectrum in the universe, is the operative dispenser. The wave-lengths of this portion of the spectrum are conveniently measured in terms of Angström (Å) units. One Angström unit (Å1) is the ten-millionth part of a millimetre (10^{-7} mm.) in length.

Ultra-violet light rays are non-ionizing;[2] that is to say they do not cause the ejection of an electron from the atom through which they pass. Only those rays which are absorbed have any effect and the amount of energy expended in the atom or molecule is equal to that absorbed. In the epidermal cells this absorbed energy is transformed into photochemical processes, manifold in nature, of which the ones which concern us in this article are either erythema-producing or pigment-forming. Selective action, either erythema-producing or pigment-forming, is shown by rays of different wave-lengths within the confines of the UVL band.[3] Briefly, there are 3 main groups of wave lengths of UVL, according to Meyer,[4] viz.:

Group A: Long wave-length group, from Å 3,900 to Å 3,200 present in sunlight and the light from carbon arc-lamps; this band does not cause erythema; pigmentation is slow in developing.

Group B: Medium wave-length group, from Å 3,200 to Å 2,800, present in sunlight, and the light from carbon arc-lamps and mercury vapour lamps; produces erythema.

Group C: Short wave-length group, Å 2,800 to Å 1,800; not present in sunlight or the light from carbon arc-lamps; but present in that from some types of mercury vapour lamps; does not produce erythema; pigmentation is early and of a greyish lustreless tint.[4]

Other effects of certain wave-lengths of UVL, i.e. carcinogenic, histamine-producing, bactericidal, etc. hardly fall within the scope of this article.

Zierz distinguishes 2 kinds of pigmentation, viz.:

1. Pigmentation produced by wave-lengths below Å 3,150. This is slow in developing and is called 'indirect' pigmentation because it follows on erythema and fades with subsequent desquamation.

2. Pigmentation due to wave lengths from Å 3,150 to Å 4,000; this he calls 'direct' pigmentation since it comes on fairly soon (about 1 hour) and is more lasting. It is supposed to be due to the oxidization of already existing, pre-formed melanin.

THE MELANOCYTE

The melanocyte is derived from the primitive neural crest, from which it emigrates in uterine life to settle in certain selected sites, viz. (1) the basal layer of the epidermis and mucous membranes at the dermo-epidermal junction, (2) the corresponding site in hair bulbs, (3) the uveal tract of the eye, and (4) the meninges of the brain, notably the leptomeninges.

Sometimes the melanocytes fail to reach their destination in the skin. In some racial types, chiefly mongolian and negroid, they fall just short of it and form large masses, usually in the lumbosacral region—the so-called mongolian spot, or smaller agglomerations halt in the upper dermis to constitute the blue naevus of Jadassohn. The former usually disappears in early life; the latter persists, but is not associated with malignancy. The proper setting for the epidermal melanocyte is the basal layer. Every 4th or 5th cell of this layer is a melanocyte and since, at times, the dark granules of melanin are concentrated round the nucleus, leaving the cytoplasm free, they were named 'clear cells'. Unlike the ordinary basal cell, the keratinocyte, the melanocytes possess numerous fine dendritic tubules, which spread out amongst the prickle cells of the Malphigian layers and convey to them the pigment, melanin. Thus, the melanocyte is really a secretory cell and its function is not only to manufacture the deeply pigmented granules of melanin but to supply the other epidermal cells with this protective substance. Melanin granules, in the form of dust-like particles, are found not only within the cells, but also lying free in the corneal layer in dark-skinned individuals. In

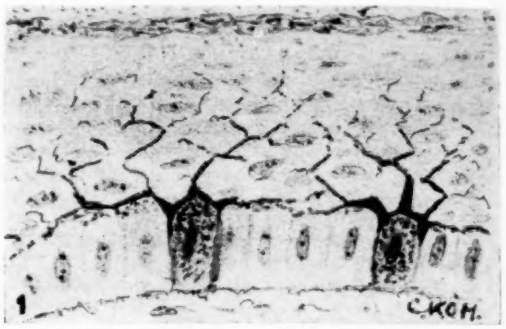


Fig. 1. Semi-diagrammatic. Two melanocytes are shown in the basal layer of the epidermis with their dendrites conveying granules of melanin. In some stages of melanin synthesis the granules are colourless.

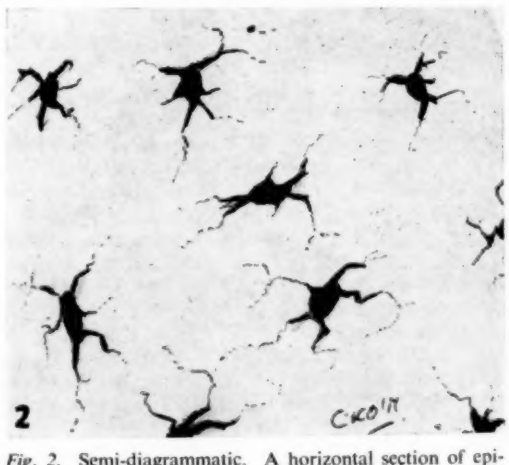


Fig. 2. Semi-diagrammatic. A horizontal section of epidermis at the level of the basal layer showing the syncytial arrangement of melanocytes.

fair-skinned people they accumulate after exposure to sunlight or as the result of other stimuli.

The distribution of the melanocyte population throughout the epidermis varies in density, being more marked in exposed areas such as the forehead than, say, on the inner aspect of the thigh. The total number has been estimated at the figure 2×10^9 with an average of 1,560 per sq. mm. The following figures illustrate this varying density in different regions of the body; they are given in mean numbers per square millimetre:[1]

Forehead	2,010 ± 210
Neck	1,400 ± 220
Thigh	1,000 ± 70
Prepuce	2,100 ± 280
Dorsum of foot	1,420 — 2,840 (two estimates)

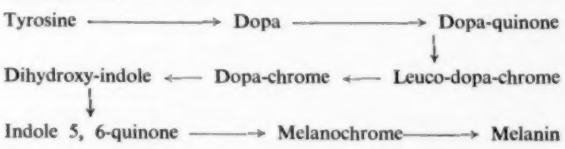
Melanocytes are more numerous on the epidermal ridges than in the corresponding valleys and, although individual variations doubtless exist, on the whole the total number is much the same in all races. The white man has as many as the dark man. He actually has more on his forehead than the negro has on the inside of his thigh. The albino has as many as either but their functional capacity is negligible. It is the differences in activity of the melanocytes rather than variations in total numbers, whether due to racial, individual or physiological factors, that make up the diverse gradations in skin pigmentation. The entire epidermal melanocytic system should be visualized as a close network of branching cells situated on the horizontal plane of the dermo-epidermal junction and forming an intricate lace-like pattern that can only be seen after special staining.

FUNCTION OF MELANOCYTES

The production of melanin by the melanocytes is the result of highly specialized and complicated intracellular activity. Much of our knowledge on the point has been gained by studies of mammalian and frog skin. Much remains still to be learnt. It is known, however, that enzymes play a dominant part. The increased pigmentation of the skin following exposure to sunlight is not due to an increase in the number of melanocytes but to an increase in melanin production by those already present. Three factors are chiefly concerned, viz. (1) a foundation substance, *tyrosine*, an amino-acid from which melanin is synthesized, (2) an enzyme, in this instance *tyrosinase*, which sparks off the process, and (3) an exciting stimulus, which normally in sun tanning is a band of UVL rays, its exact place in the UVL spectrum not having yet been accurately determined. We could compare these 3 factors roughly with the petrol, the sparking system and the battery of a motor-car.

Both tyrosine and tyrosinase are normally present in the melanocyte, the former in molecular form in the cytoplasm and the latter situated on the surface of the so-called melanin granules. Melanin itself is a protein conjugate formed by the union of a quinioid polymer, *indole 5, 6-quinone* with protein. It is the final stage of a complex chain of metabolic events. One of the intermediate stages, the second in the series, is a substance called *dihydroxy-phenylalanine*, dopa for short. Bloch was one of the first to experiment with the substance. He found that when sections of human skin were immersed in a solution of dopa at pH 7·4 the melanocytes and their processes were stained black. The reaction is not a specific one, because leukocytes, under the same conditions, show similar darkening. The so-called dopa reaction is a landmark in the development of the histochemistry of the skin and is still a serviceable laboratory test.

Starting with the amino-acid tyrosine, which, with the enzyme tyrosinase, is a fundamental prerequisite, the successive steps in the production of melanin are shown in the following diagram; for the sake of clarity the structural formulae are omitted:



Oxygen, together with tyrosinase, is necessary for the completion of the synthesis and is supplied by the cell itself. Some of the changes or reactions occur rapidly, others slowly. Some are certainly enzymatic, others may not be. And it is believed that oxidation is an essential process, for some of the stages at least.

The elaboration of melanin from its precursor tyrosine does not proceed in a constant automatic manner. On the contrary, it is subject to controls and checks and is necessarily dependent on the availability of tyrosine and tyrosinase. In the albino there is no lack of melanocytes or tyrosine; but there is an inherited shortage of tyrosinase. We might compare the position of the albino in this respect to that of a motor-car in which the engine is in working order and an adequate supply of petrol is available but the ignition system is faulty or absent. Certain chemicals, too, by combining with the copper in tyrosinase deprive this enzyme of an essential, thus halting the course of events at its beginnings and so seriously interfering with the production of melanin. Furthermore, certain substances—hormones and such like—exert through the circulation a degree of remote control over the complex happenings of melanogenesis.

Leaving out of consideration, for the moment, the initiating effect of UVL radiation or other stimulus, there are other operative factors which can be classified into two main categories, viz.:

(A) Substances produced in remote parts of the body and subsequently brought in contact with the pigment-forming cells; these substances determine the *distribution* pattern of melanin granules within the melanocytes.

(B) Factors dependent on intracellular, enzymatic activity determining the *amount* of melanin.

EFFECT ON MELANOGENESIS BY HORMONES AND OTHER SUBSTANCES

Experiments on frogs and marine species showed that both removal of the pituitary gland and injection of its extracts exert a dominant influence on skin pigmentation. Injection of an extract of hog's pituitary has a darkening effect on frog's skin. In humans the same effect is produced. Recently two hormones, alpha and beta melanotic stimulating hormones (MSH), have been isolated from hog's pituitary gland. Chemically, they belong to the class of polypeptides. Similar hormones have been isolated from the pituitary gland of other mammals, though certain structural differ-

ences exist. It seems certain, then, that a melanotic stimulating hormone (MSH) is secreted by the pituitary which has the property of darkening the skin by its action on melanocytes. But the action of MSH does not proceed uncontrolled. Removal of the adrenal glands or suppression of their function by disease, as in Addison's disease for instance, leads to bronzing of the skin through uncontrolled pigmentation.

It is believed that the adrenals exert an antagonistic effect to the pituitary and that the balance between these reciprocal functions determines the degree of skin pigmentation at any time.[6] The clinical phenomenon of increased pigmentation, in conditions where the normal functioning of the adrenals is interfered with, makes this belief more than a reasonable assumption. Sex hormones, too, in a still unexplained manner, have a certain stimulating effect on melanin production. Pillsbury[6] records, for instance, that eunuchs fail to tan when exposed to ultra-violet light unless they are given male sex hormones at the same time. The increased pigmentation during pregnancy is probably the result of a direct stimulation of the MSH function of the anterior pituitary by circulating hormones.

The production of melanin seems to be a protective mechanism, though at first sight it is difficult to see how particles of 1 μ size, with measurable spaces between the particles, could form an effective barrier against UVL wave-lengths of much smaller dimensions. The response follows exposure to such stimuli as sunlight, ionizing radiations like X-rays, and inflammatory processes in the skin itself, such as dermatitis, lichen planus and discoid lupus erythematosus. But what is not known for certain is how exactly, say, UVL stimulates the process of melanogenesis. It is suggested that it does so rather by suppressing inhibitors, since the enzyme tyrosinase is said not to function optimally under the usual physiological conditions. Although, like other epithelial cells, the melanocytes multiply and are cast off or form large aggregates, in both simple and malignant conditions, the chief factor in increased pigmentation, it must be repeated, is not an increase in the number of melanocytes so much as an increase in the amount and distribution of melanin.

INTRACELLULAR, ENZYMATIC FACTORS AFFECTING MELANOGENESIS

Each individual melanocyte has within itself the 3 necessary units for the elaboration of melanin, viz.: (1) coarse so-called melanin granules, which form the foundation, as it were, on which the final pigment is built, (2) tyrosine, the amino-acid, which through a series of changes eventually becomes the dark substance melanin, and (3) the enzyme tyrosinase, which is the sparking-off stimulus that starts the whole intricate chemical process. Tyrosinase belongs to a group of copper-containing enzymes which catalyse the oxidation of both mono- and dihydric phenols. In mammals it catalyses the hydroxylation of tyrosine to dopa and the further hydroxylation of dopa to dopa-quinone. Both of these steps are essential preliminaries to the sequence of events ending in melanin.

A further indispensable condition is the reduction of the copper in tyrosinase from the cupric to the cuprous state. It follows, then, that any substance, and there are many, which by forming bonds with the copper prevents this reduction acts as an inhibitor and holds up the whole process of melanogenesis from the very start. Mercury, gold, BAL, sulph-hydryl groups, etc. unite avidly with copper. They are all therefore inhibitors of pigmentation. Thus is explained the hypopigmentation noted in patients under treatment with BAL and the rationale of the use of ammoniated mercury for the treatment of excessive pigmentation. Similarly, in a roundabout way, the reason for the hyperpigmentation sometimes noted in arsenic therapy becomes clear. Arsenic unites with sulph-hydryl groups readily, before they get a chance to form bonds with the copper in tyrosinase, and this removal of the potent inhibitor sulph-hydryl leaves the field clear for melanogenesis to proceed apace. It is noteworthy that these two commonly encountered metals have directly opposite effects. Mercury decreases pigmentation, arsenic increases it, both by playing antagonistic roles *vis-à-vis* the copper atoms in tyrosinase. Hydroquinone is another inhibitor of tyrosinase activity. Its monobenzyl ether is met with in the rubber industry, where contact with it is a well-known occupational hazard for negro workers in the USA, causing bleaching of the hands.

The utter dependence of melanin synthesis on enzymatic intracellular activity is beautifully illustrated in the condition phenylpyruvic-oligophrenia. Sufferers from this rare condition tan poorly and are subject to eczema and other defects. The background is a breakdown in the normal synthesis of tyrosine brought about in the following manner: Phenylalanine, an essential amino-acid, is the precursor of tyrosine. It is not synthesized in the human body but is ingested in the food. An enzyme phenylalaninase, normally present in the liver, hydroxylates phenylalanine to tyrosine. But in phenylpyruvic-oligophrenia there is a congenital absence of this enzyme, or some alteration in its quality, so that there results a superabundance of phenylalanine and a corresponding deficiency of tyrosine, the ground substance for the synthesis of melanin. About 10% of the ingested phenylalanine is synthesized to tyrosine by means other than the liver, so that the serum shows normal values; but there remains a superfluity of phenylalanine, and the organism attempts to get rid of it by excreting it as pyruvic acid and other similar compounds in the urine, which is coloured red in such circumstances by the addition of ferric chloride. Meanwhile the enzyme, tyrosinase, has a greater affinity for phenylalanine than for its usual partner, tyrosine; thus the production of melanin is sabotaged at the very first stage.

THE EFFECT OF THE INTRACELLULAR DISTRIBUTION OF MELANIN GRANULES

The tolerance of the negro skin for sunlight is due, not only to the presence of larger, coarser granules of melanin in the melanocytes themselves, but also to the presence of these granules in other cells of the epidermis and even in the corneal layer, which is itself thicker than in the white-skinned person. The melanin granules, it will be remembered, are conveyed to the other epidermal cells through the dendritic processes of the melanocytes and move to the surface of the skin with the continual growth of the epidermis. Furthermore, the pigmentation following, for instance, exposure to sunlight, may be more apparent than real, for the same effect may be produced either by an actual increase in the number of melanin granules within the cell,

or by a rearrangement of the granules without any increase in number. When the melanin granules are widely dispersed throughout the cytoplasm an impression of increased darkening is caused, but when the same number are clumped together on the nucleus the opposite effect is produced.

If a solution of MSH is added to frog's skin the movement of the melanin granules outwards from the nucleus can be seen. MSH therefore causes darkening of the cell by the dispersion of the granules which renders the cell more opaque. Other substances that have a similar dispersal effect are: ACTH, caffeine, apresoline, mesantoin, progesterone. Recently a substance that has a contrary effect, that is, clumping the melanin granules, with a consequent lightening of the cell, has been isolated from the pineal glands of cows. This hormone, probably originating from

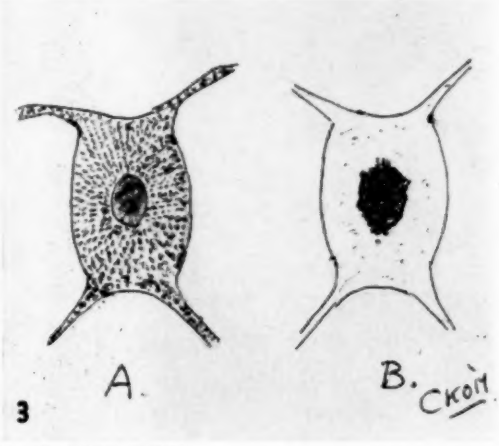


Fig. 3. Diagrammatic.

A. A melanocyte in which the granules are dispersed throughout the cell protoplasm, rendering it dark and almost opaque. Action of MSH.

B. The same cell, in which the melanin granules are clustered on the surface of the nucleus. The cell is clear. Action of melatonin.

the amino-acid tryptophane, has been named melatonin. It has been found in human pineal glands as well as in peripheral nerves, where it may possibly have something to do with the development of vitiligo. Other lightening agents causing clumping of the granules on the nucleus are nor-adrenaline, adrenaline, acetylcholine, serotonin, diamox. None of these are as powerful in effect as melatonin. The members of these two antagonistic groups are set out as follows:

Substances darkening the cell by dispersal of granules	*Substances causing lightening of the cell by clumping of granules*
MSH both alpha and beta (pituitary)	Melatonin (pineal)
ACTH	Nor-adrenaline
Caffeine	Adrenaline
Apresoline	Acetylcholine
Mesantoin	Serotonin
Progesterone	Diamox
and others	Tri-iodothyronine and others

RÉSUMÉ

The complete process of pigment formation may be conveniently condensed in the following statements:

1. The synthesis of the skin pigment melanin is carried out by the melanocyte, which is situated in the basal layer of the epidermis; it migrates from the neural crest to the skin and other sites during intra-uterine life.

2. The number of melanocytes per sq. mm. of skin varies according to the site, being most numerous in the exposed areas; the average number is 1,560.

3. Increased pigmentation is presumably a normal protective response to agents such as sunlight, UVL, X-rays, inflammatory processes, etc. Accompanying thickening of the corneal layer, as in negroes, gives increased protection.

4. The amino-acid tyrosine is the foundation on which the structure of melanin synthesis is built. The enzyme tyrosinase is an indispensable factor. Lack of either of these or interference with their functions leads to pigmentary disorders. Oxygen is necessary in some stages.

5. A hormone secreted by the anterior pituitary gland MSH stimulates melanin production. The adrenals have an antagonistic effect.

6. Increased pigmentation is not so much due to an increase in the number of melanocytes as to an increase in the amount of melanin formed and to the intracellular arrangement of the melanin granules.

7. MSH and other substances cause dispersion of the granules; melatonin, a secretion of the pineal gland, and other substances, e.g. adrenaline, have an opposite effect. Dispersal of granules darkens the melanocyte; clumping of granules make it less opaque.

SUMMARY

The role of the melanocyte in the synthesis of melanin is discussed and the importance of the enzyme tyrosinase is stressed. Mention is made of the various factors, both intracellular and extracellular, which speed up or hinder the process. A comparison is made between those substances which darken the melanocytes by dispersing the melanin granules and those which lighten them by clumping the granules on the cell nucleus.

The writer re-affirms his special indebtedness to the various contributors to the special number of the *Journal of Investigative Dermatology*[1] dealing with this subject. The fruits of their laborious researches are here presented in abridged form to the general medical reader.

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FAMILIAL CHRONIC HYPERTROPHIC POLYNEUROPATHY WITH PARALYSIS OF THE EXTREMITIES IN COLD WEATHER

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The syndrome of muscular atrophy, sensory loss and absence of tendon jerks in the extremities, associated with palpable or visible thickening of peripheral nerves, was first recognized as a clinical entity by Déjerine and Sottas[11] in 1893. They described the disease in a brother and sister, and added an earlier reported case of Gombault and Mallet[16] which had been regarded as an unusual case of tabes dorsalis. In 1906, Déjerine and Thomas[12] confirmed the pathological findings of hypertrophic interstitial neuritis in another case. Wolf[34] surveyed the literature in 1931 and managed to collect 40 cases up to that time. Several more have since been added.[21] The familial nature of the disease was emphasized by Brasch[8] in 1904 and a number of affected families have since been reported.[22,17,35,32,15,30] Other cases have occurred sporadically.

The disease may manifest itself at any time of life, varying from childhood to middle age. The sexes are equally affected. The disease is non-inflammatory and the term chronic hypertrophic polyneuropathy is used in preference to that of chronic hypertrophic interstitial neuritis, progressive hypertrophic neuritis, or maladie de Déjerine-Sottas.

The condition is insidious in onset though a long history of cold extremities is usually available. With gradual destruction of both motor and sensory components of the peripheral nerve, weakness and sensory loss in the extremities progresses. The degree of sensory and motor impairment, however, need not be equal, some cases having an almost entirely motor manifestation. Trophic ulceration is uncommon and cranial nerves are rarely affected. Root pains may be troublesome. The hypertrophy of the nerves bears no relationship to the degree of motor or sensory involvement. Recurrences and remissions of symptoms have been reported.[29,25,19]

The nerves are the seat of cellular proliferation and connective tissue is laid down in a lamellar fashion around single nerve fibres, giving an 'onion skin' appearance. The collagen tissue is derived from the Schwann cells and is quite distinct from the endoneurium.[22] However, both Schwann sheath and endoneurium may be affected. The process involves the nerve tissue from the roots to the periphery in varying degrees. Spinal ganglia may show involvement, with atrophy and fibrous overgrowth. Myelin fragmentation and the presence of 'plasmic swellings' have been demontrated.[15] Some cases may show involvement of the posterior columns, with degeneration and sclerosis.

The condition is slowly progressive and varies enormously from case to case.

The following family is placed on record not only because of the rarity of the disorder but also to describe the severe autonomic disturbance occurring with minor fluctuations in environmental temperature, resulting directly or indirectly in gross deterioration in sensory perception and flaccid paralysis of the extremities, both reversible on rewarming.

CASE REPORT

Mr. C.B., aged 28 and the father of 3 children, suffered from pain on walking, and at rest when cold. The pain had been present for the past year in the right foot, where a discharging perforating ulcer had developed during the past 6 months. At the age of 16 he noticed calluses forming under the metatarsal heads of both feet. The feet had become deformed since the age of 9 years, the deformity being that of pes cavus. For the past 3 years the patient had noticed a weakness of extremities during the winter months, particularly marked on very cold days. At times he was quite unable to walk or use his hands. The weakness was accompanied by a numbness of the feet. There has been a gradual loss

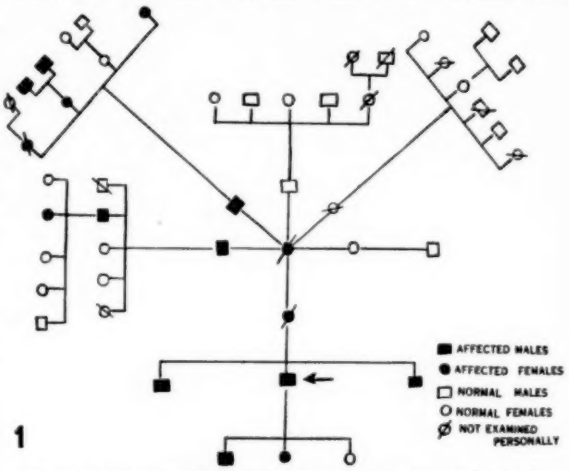

Fig. 1. Showing transmission through several generations of the disorder, with muscular atrophy, pes cavus and thickened nerves.

of weight from 212 lb. to 160 lb. over the past 3 years. He perspired profusely and had complained of cold extremities for years. He did not think there was anything wrong with other members of the family but on direct questioning he recalled that his mother, 2 uncles and a cousin had pes cavus. The family was investigated and numerous members were found to be involved (Fig. 1).

Examination

Blood pressure 140/100 mm. Hg. Cranial nerves intact, fundi normal. Marked atrophy of the small muscles of the hands and feet and, to a lesser extent, of the arms and legs. Perforating ulcer over head of 5th right metatarsal. The reflexes were present and equal coordination was normal, and in the warmth of the ward (70°F) muscle power and sensation were normal. There was palpable thickening of the peripheral nerves. The cervical cutaneous nerves stood out like cords as the head was turned putting them on stretch.

Haemoglobin, 15 g./100 ml. Leucocyte count, 4,900/c.mm. Differential count, normal. Blood urea, 15 mg./100 ml. Serum G-O transaminase, 51 units/100 ml. Serum glutamic-pyruvic transaminase, 75 units/100 ml. Serum sodium, 132 mEq./litre. Serum magnesium, 1·8 mEq./litre. Serum creatinine, 0·8 mg./100 ml. Wasserman reaction negative. Random blood sugar, 108 mg./100 ml. Serum calcium, 4·7 mEq./litre. Plasma inorganic phosphorus, 3·8 mg./100 ml. Total serum protein, 8·3 g./100 ml.; albumin, 3·04 g./100 ml.; alpha-1 globulin, 0·76 g./100 ml.; alpha-2 globulin, 1·10 g./100 ml.; beta globulin, 1·68 g./100 ml.; gamma globulin, 1·72 g./100 ml. Serum protein-bound iodine, 4·0 μg./100 ml. Erythrocyte sedimentation rate, 24 mm. in first hour.

The cultivation of the pus from the ulcer showed infection with *Staphylococcus aureus* sensitive to chloromycetin and erythromycin.

The average 24-hour urinary volume was 2,500 ml., containing sodium 57 mEq./litre, potassium 11 mEq./litre, phosphorus 650 mg., and creatinine 1,300 mg., of which 50 mg. was creatine.

ECG normal. X-rays of chest and skull normal.

X-rays of the right foot showed marked destruction and sclerosis of the 5th metatarsal bone.

The posterior auricular nerve was biopsied and revealed the following change: (1) Thickening of the perineurium, (2) definite collagenous thickening around many of the individual nerve fibres, (3) thinning of the myelin sheaths, and (4) in longitudinal sections a separation of the nerve fibres with occasional strands of collagen between these structures.

On muscle biopsy a few abnormal small fibres were seen, with an increased number of dark small nuclei.

Skin biopsy showed evidence of swelling of the endothelial cells of some of the small blood vessels. At one level a definite acute vasculitis was evident in some small vessels in the deep part of the dermis.

Electromyographs showed normal motor unit activity in the proximal muscles. The small muscles of the hand produced a mixed pattern on maximum contracting, indicating a 40% reduction in contracting muscle fibres.

When the patient was re-examined after walking about the hospital garden on a cold winter morning of 45°F, marked weakness of the legs and complete loss of sensation to all modalities was found, involving the right foot and leg and the left foot. This rapidly disappeared when he re-entered the warm hospital wards. The patient was constantly perspiring, most noticeably in the hands and feet.

Skin temperatures were recorded at various sites before and after reflex lumbar heating and after the administration of 25 mg. of priscol by mouth. The results are shown in the following table (in °F):

Skin Tested	*Resting*	*½ hour after lumbar heating*	*½ hour after ora. priscol*
Dorsum of right arm ..	85·0	85·6	89·0
Dorsum of right hand ..	75·2	80·0	82·5
Ventral surface of left arm	86·2	86·4	88·3
Left palm	75·6	88·0	88·0
Front of right leg ..	83·5	81·6	88·0
Dorsum of right foot ..	84·6	87·0	93·8
Back of left leg	80·0	80·0	90·2
Sole of left foot	76·8	78·4	89·0
Dorsum of left foot ..	76·8	80·2	90·0

Electromyographic studies on the small muscles of the hand were repeated during cooling of the limb; the results are seen in the tracings in Fig. 2, which show the falling out of motor unit activity and the decreasing potentials. At 68°F there was no recordable activity on attempted contraction of the muscles. During this stage there was no response of the muscle to direct electrical stimulation. There were also no changes in the electrolytic content of the blood. Kymographic studies were also carried out at various temperatures in a water bath, the results of which are shown by the tracings in Fig. 3, which demonstrate the weakness occurring in the muscle of the forearm at lower temperatures. The arm was submerged in a water bath, and a 5 lb. weight attached to the fingers was elevated as the hand was closed; the excursions of the weight were recorded on a rotating drum.

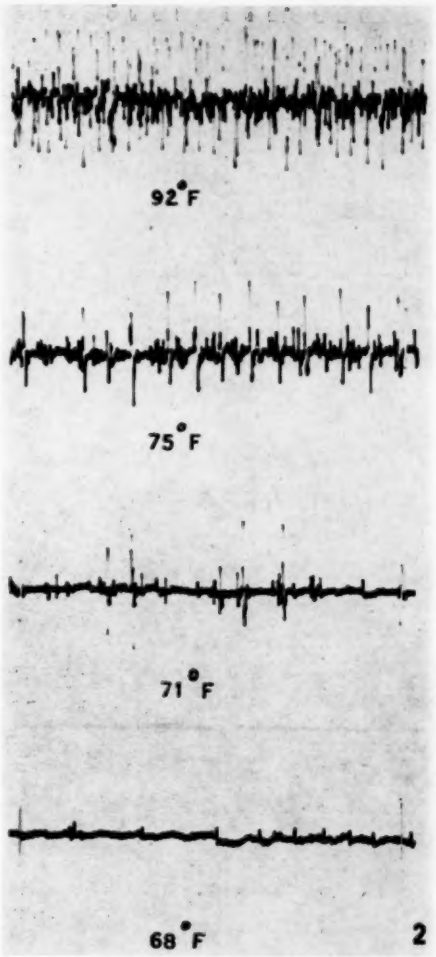

Fig. 2. First dorsal interosseous, maximum contractions at various temperatures. Voltage 100 μv./mm. Paper speed 20 msec./mm.

DISCUSSION

There are several reports of cases where hypertrophic neuritis has been associated with other features, e.g. kyphoscoliosis, intention tremor, dysarthria, fasciculation of muscle, and sensory ataxia. It is not surprising that some cases of this disease have been misdiagnosed as tabes dorsalis, like Gombault and Mallet's original case in 1889.[16] Others have been confused with Friedreich's ataxia or peroneal muscular atrophy.

Refsum[27,28] described a syndrome occurring in both adults and children, which he called 'heredopathia atactica polyneuritiformis', and Ashenhurst *et al.*[1] have recently reported a further 3 cases occurring in one family. This syndrome is characterized by atypical retinitis pigmentosa, chronic progressive polyneuritis, high protein in the CSF, with cyto-albuminological dissociation, signs of cerebellar dysfunction, occasional nerve deafness, abnormal pupillary reactions, and anosmia. Skin changes may also occur in the form of ichthyosis, as well as ECG conduction abnormalities. Changes characteristic of hypertrophic interstitial neuritis have been reported in the peripheral nerves in one case.[31]

It is possible that several of the cases of hypertrophic polyneuritis in the literature showing kyphoscoliosis,[16,32,7] or kyphoscoliosis with nystagmus[11] or with intention tremor,[36,10] are examples of a mild form of Refsum's syndrome. It may, in fact, be argued that Refsum's syndrome on the one hand, and progressive hypertrophic neuropathy on the other, represent two extremes or near-extremes of a particular spectrum of disorder.

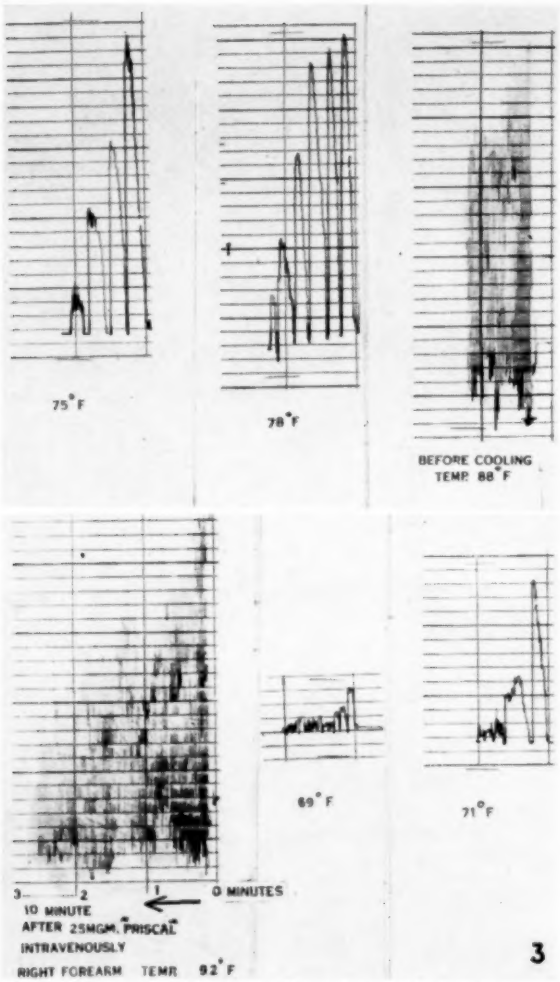

Fig. 3. Drum rotating from right to left recording repetitive grasping movements of the right hand elevating a 5 lb. weight.

As stated earlier, trophic disturbance is rare in hypertrophic polyneuropathy, whereas it is not an uncommon feature of certain other disorders, some of which may be familial.

In 1913 Price[26] described a disease affecting the spinal cord with the production of central cavities. This was later regarded as a form of gliosis, often associated with a peripheral neuritis and having a familial tendency. It is probably identical with a condition described by Morvan[23] 30 years earlier as affecting the fishermen of Brittany.

Syringomyelia has long been recognized as a cause of trophic ulceration. This condition, and also neurofibromatosis and tuberous sclerosis have been considered to be a spongioblastosis with resultant incomplete developmental closure of the spinal cord.[3,9] All three of these conditions may occur in families.

The condition of familial perforating ulcer of the foot was considered by Hicks[19] to be a separate clinical entity. Besides the trophic ulceration of the feet there was often an associated deafness which is of particular interest because of this occurrence of deafness in the Refsum syndrome. Thevenard[33] also recorded familial perforating ulcer of the foot as a condition distinct from lumbodorsal syringomyelia. Despite these opinions, however, typical familial cases of perforating ulcer have been observed[24,4] and later found to be associated with typical or atypical syringomyelia.

Trophic ulceration may complicate many diseases of the peripheral sensory nervous system; it may be associated with leprosy, syphilis, traumatic lesions, primary amyloidosis, and occasionally peroneal muscular atrophy.[14] Several authors have commented upon the occurrence of associated vascular disease in polyneuropathy.[20] Van Bogaert[6] has considered vascular lesions in some cases to be secondary to a disorder of the peripheral nervous system, and that a vicious circle is thus established.

Denny-Brown,[13] in his anatomical study of members of a family with perforating ulcers of the feet, emphasized the degeneration of the spinal ganglia and accumulation in them of a hyaline substance, and an associated secondary amyloid degeneration of the blood vessels. Their case also showed degeneration of the posterior columns, posterior roots and peripheral nerves. Van Bogaert[5] described further cases of 'hereditary polyganglionic radicular disease', affecting both nerves and vascular tissue, which showed deposition of a hyaline substance that was distinct from amyloid. He found rarefaction of the axis cylinders and fibrosis of the perineurium, with subintimal proliferation of the small arterioles.

There is another group of disorders which may give rise to trophic disturbances. This group includes the case with dysfunctions presumably of the sympathetic nervous system, e.g. Raynaud's disease and acrodynia. In these cases, besides the hypo- or hyperaesthesia, there is often hyperhidrosis, coldness, swelling and pain in the affected extremity.

CONCLUSION

The family presented in this paper shows no evidence of retinitis pigmentosa, kyphoscoliosis, pathology of the dorsal column, intention tremor, deafness, or elevation of the protein in the CSF; they are considered to be typical cases of hypertrophic polyneuropathy associated with a severe peripheral sympathetic nervous overactivity, resulting in vascular changes which establish a vicious circle as regards the trophic integrity of the extremities.

The sensory changes in this case have been largely prevented by the continuous administration of priscol in doses of 50 mg. *t.d.s.* This regime has seen the patient through the winter months and now with the warmer weather he has been able to do without the vasodilator. With the aid of antibiotics the ulcer has almost healed.

SUMMARY

A case of hypertrophic polyneuropathy presenting with a perforating ulcer of the foot and a periodic flaccid paralysis of the extremities during cold weather is presented. Other members of the family were examined and several members of live generations were found to be affected.

Other familial conditions with either hypertrophic polyneuropathy or perforating ulcers of the feet are discussed.

I wish to thank Dr. A. Agranat, Senior Physician, and Dr. K. Mills, Superintendent, Johannesburg General Hospital, for their cooperation; also Dr. S. Levin, paediatrician, for referring the original case and Mr. H. Kruger, of the Medical School of the University of the Witwatersrand, for the photographs. The electromyography was carried out by kind permission of the Princess Nursing Home neurosurgical unit. For the histological report I thank Dr. J. C. E. Kaufmann.

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A MALIGNANT LYMPHOMA SHOWING THE HISTOLOGICAL FEATURES OF MULTIPLE MYELOMATOSIS, HODGKIN'S DISEASE, AND RETICULUM-CELL SARCOMA

REPORT OF A CASE WITH A REVIEW OF THE LITERATURE

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South African Institute for Medical Research and Baragwanath Hospital, Johannesburg

It has long been known that there is an interrelationship between the various lymphomata. There have been many case reports illustrating the numerous manifestations of reticulo-endothelial diseases and the simultaneous occurrence of different forms of these diseases.[1-6]

This brief report deals with a case in which there was neoplastic proliferation of plasma cells and reticulum cells with foci manifesting the histological picture of Hodgkin's disease. Tuberculous lymphadenitis was an additional finding.

CASE REPORT

A.M., a 40-year-old Bantu female was admitted to Baragwanath hospital on 17 November 1958 complaining of generalized body pains, abdominal pain, and a swelling in the left axilla of about 4 months' duration.

On examination she was found to be extremely anaemic and thin with evidence of marked weight loss. The blood pressure was 120/80 mm.Hg and the pulse rate was 80 per minute. A soft systolic murmur was heard at the base of the heart and a third heart sound at the apex. The liver was enlarged to 2 cm. below the costal margin. A swelling was present in the left axilla 4 - 5 cm. in diameter and the clinical impression was that of matted lymph nodes. Laboratory investigations included: haemoglobin of 4·7 g.%, haematocrit 19%, mean corpuscular haemoglobin concentration 25, and leucocytes 9,600 per c.mm.

A transfusion of 2 pints of blood was given. Bone marrow examination on 21 November revealed a conspicuous plasmacytosis, the plasma cells being of the mature variety. Erythropoiesis was normoblastic and active and some of the normoblasts showed evidence of iron deficiency. There was an increase in the amount of stainable iron in the marrow and these findings were interpreted as a non-sideropenic form of hypochromic anaemia, such as occurs in chronic infection, malignant disease, etc.

A biopsy was performed on the axillary lymph nodes. Microscopic examination showed an enlarged lymph node in which there were a few small tuberculous granulomata (Fig. 1). The greater part of the node, however, showed proliferation of reticulum cells with large numbers of plasma cells, some of which were atypical and contained several nuclei, prominent nucleoli and not infrequent mitoses. It was suggested that the patient be investigated for the possibility of myelomatosis. The patient was then given streptomycin 1 g. daily, by intramuscular injection, rimifon 600 mg. daily by mouth, and urethane 150 mg. daily.

Examination of the urine for Bence Jones protein was negative on 2 occasions and microscopic examination of a centrifuged specimen showed hyaline and granular casts, occasional erythrocytes, and 2 - 4 polymorphonuclear leucocytes per high-power field. Electrophoretic studies of the serum proteins showed the following: total protein 7·5 g.%, albumin 13·8% (1·03 g.%), alpha 1 globulin 8·7% (0·65 g.%), alpha 2 globulin 14·5% (1·09 g.%), beta globulin 14·9% (1·12 g.%), and gamma globulin 48·1% (3·61 g.%).

On 22 December the patient had an epistaxis which necessitated plugging of the nose.

The bone marrow examination was repeated on 24 December. There was a very marked plasmacytosis, some of the plasma cells occurring in sheets. The majority of the plasma cells were mature, but some cells resembling 'myeloma cells' were observed. X-ray examination of the chest showed clear lung fields and a soft tissue mass in the left axilla. The skull, pelvis, and right femur showed no translucent areas. A blood count showed no significant change and another transfusion of 3 pints of blood was given. Blood films examined on 13 January 1959 showed 64% neutrophils, 6% monocytes, 26% lymphocytes and 4% plasma cells.

A further transfusion of 2 pints of blood was given on 14 January. Throughout her stay in hospital the patient had remittent pyrexia between 90°F and 101°F. On 20 January she started deteriorating rapidly, and died on 22 January, 9 weeks after admission and 6 months after the onset of symptoms.

Autopsy Findings

The body was that of a markedly emaciated female. An irregular firm mass about 8 cm. in diameter was present in the left axilla. Both parotid glands were enlarged to 5 cm. in diameter, and on section, exuded purulent material.

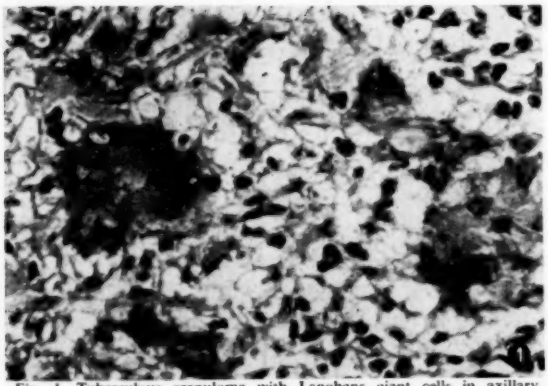

Fig. 1. Tuberculous granuloma with Langhans giant cells in axillary lymph node (haematoxylin and eosin × 480).

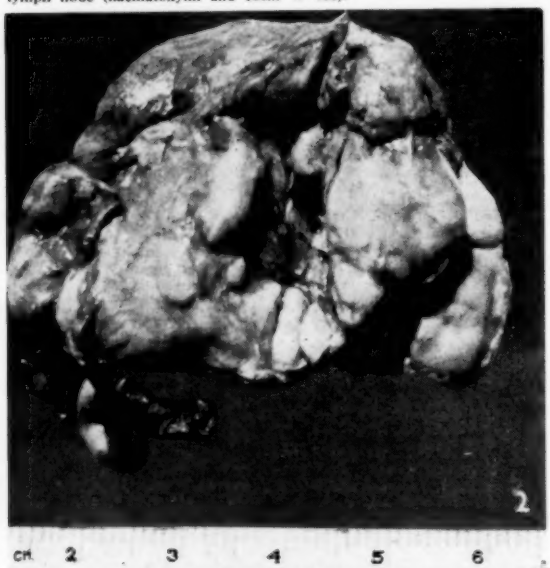

Fig. 2. Enlarged matted axillary lymph nodes.

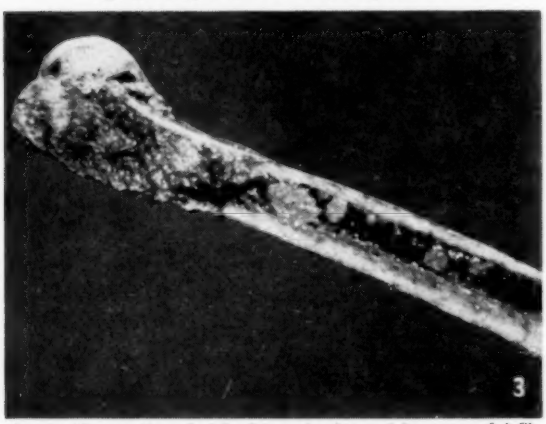

Fig. 3. Cross-section of right femur showing nodular areas of infiltration throughout the bone marrow.

The major morbid anatomical findings were confined to the reticulo-endothelial system.

The mass dissected from the left axilla consisted of enlarged matted lymph nodes measuring 9×4×3 cm. in size. On section they were fairly firm in consistency and pale yellowish-white in colour (Fig. 2).

The left supraclavicular lymph nodes, para-aortic lymph nodes and mesenteric nodes presented a similar appearance.

The spleen (250 g.) was enlarged and on section showed the presence of a well-demarcated yellowish-white subcapsular area 1½ cm. in diameter. The remainder of the pulp had a mottled appearance with yellowish foci alternating with the dark red pulp.

The right femur, on section, showed the presence of numerous well-circumscribed yellowish-white areas of infiltration in the red marrow and to a lesser extent in the white marrow. The distribution of the red marrow appeared normal (Fig. 3).

The remaining morbid anatomical findings were essentially negative.

Microscopic Examination

Sections of the mesenteric, para-aortic and left supraclavicular lymph nodes presented similar features. There was complete loss of the normal architectural pattern due to infiltration by large pleomorphic cells, many resembling large plasma cells with an eccentric nucleus showing clumping of the chromatin and a prominent eosinophilic nucleolus (Fig. 4). Other cells had large horse-shoe shaped nuclei while some contained as many as 5 nuclei; the multinuclear cells resembled the Reed-Sternberg cells seen in Hodgkin's disease (Figs. 5 and 6). In addition, there was considerable reticulum-cell hyperplasia and marked mitotic activity (Fig. 7).

The enlarged left axillary lymph nodes showed a similar picture to the original biopsy, with marked plasma-cell proliferation, moderate reticulum-cell hyperplasia and occasional multinucleated giant cells. Several areas showed deposition of acidophilic homogeneous material which special stains proved to be amyloid.

The spleen showed large areas of necrosis. The remainder of the parenchyma was infiltrated by atypical plasma cells and numerous giant cells of the Reed-Sternberg type. Reticulum-cell hyperplasia was also a prominent feature. Large areas of the spleen were replaced by amyloid material (Fig. 8). The liver showed areas of necrosis, some of which resembled amyloid. At the periphery of these areas there was infiltration by lymphocytes and large atypical plasma cells.

The bone marrow showed a pleomorphic cellular infiltration consisting mainly of neoplastic plasma cells (Fig. 9). In addition there were areas of necrosis and amyloid deposition.

Section of the parotid glands showed an acute suppurative parotitis. The remaining histological findings were negative.

DISCUSSION

This case demonstrates the close association between the various groups of lymphomata. It shows features of Hodgkin's disease, reticulum-cell sarcoma and multiple myelomatosis. According to Lumb[7] the primitive mesenchymal cell may differentiate into either the lymphocyte or the reticulum-cell, and neoplastic proliferations of these two cell types give rise to the lymphosarcoma and reticulum-cell sarcoma respectively. Malignant transformation of both cell types results in the histological picture of Hodgkin's disease.

According to some authors the plasma cell is derived from the reticulum-cell[8] and in view of this it is surprising that tumours showing proliferation of both these cell types are not seen more frequently.

Herbut, Miller and Erf[6] reported 6 cases that at various stages during life were diagnosed as both Hodgkin's disease and lymphosarcoma. At autopsy they showed various combinations of Hodgkin's disease, lymphosarcoma

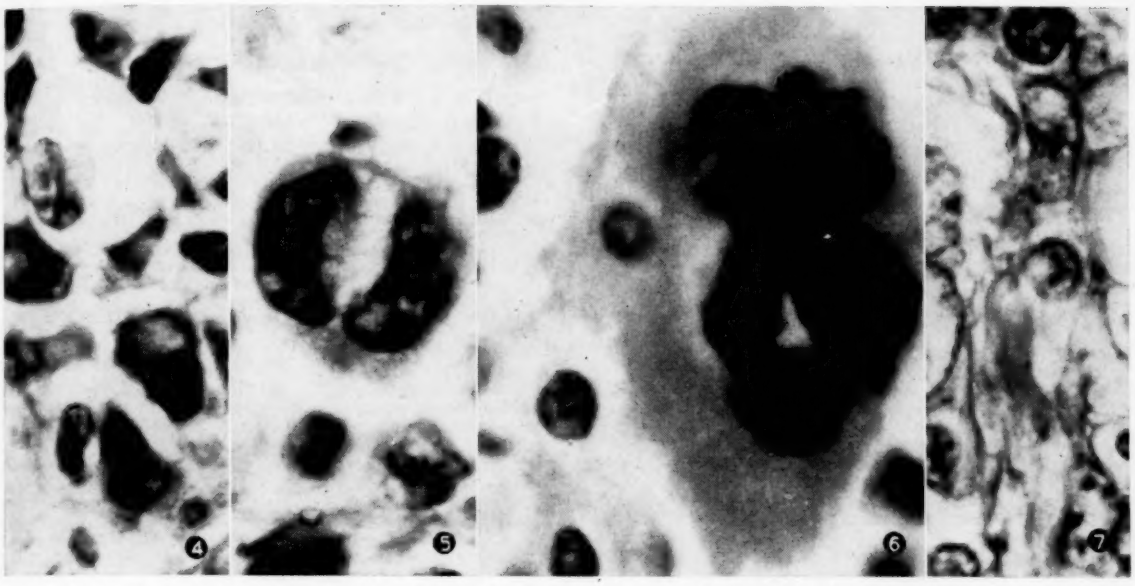

Fig. 4. Photomicrograph of an axillary lymph node showing large, atypical plasma cells (haematoxylin and eosin × 1900).
Fig. 5. Photomicrograph of a mesenteric lymph node showing a characteristic mirror-image cell (haematoxylin and eosin × 1900).
Fig. 6. Multinucleated giant cell surrounded by numerous large plasma cells (haematoxylin and eosin × 1900).
Fig. 7. A further field in the lymph node portrayed in Fig. 5, showing proliferating reticulum cells (haematoxylin and eosin × 1900).

and reticulum-cell sarcoma. They believed that these diseases are not only genetically related but are fundamentally merely phases of the same lesion. The various combinations can be explained only by considering these diseases as arising from a common stem cell and then differentiating in one direction or another according to the amount and type of stimulation as described by Miller and Turner.[9] These authors found 2 substances in increased amounts in the urine of patients suffering from Hodgkin's disease and monocytic leukaemia and separated them chemically into carbinols and noncarbinols. Guinea-pigs inoculated with the carbinols showed increased lymphopoiesis whereas those inoculated with noncarbinols showed increased myelopoiesis. Administration of the 2 products simultaneously resulted in lymphoid and reticulum-cell hyperplasia with foci resembling Hodgkin's disease.

Seife *et al.*[3] reported a case of a man diagnosed clinically as chronic lymphatic leukaemia who was subsequently found at autopsy to have Hodgkin's disease and tuberculosis as well as lymphatic leukaemia.

Co-existent myelogenous leukaemia and Hodgkin's disease has been reported by Samwick *et al.*,[5] and the interrelationship of Hodgkin's disease and other lymphatic tumours was discussed by Custer and Bernhard,[1] who analysed 1,300 lymphatic tumours. They showed a striking fluidity in histological pattern with various transitions and combinations.

The simultaneous occurrence of multiple myeloma and Hodgkin's disease in 2 patients was found by Greenberg and his associates.[2] The first case concerned a patient in whom bone-marrow punctures and lymph-node biopsies performed at the same time showed unmistakable evidence

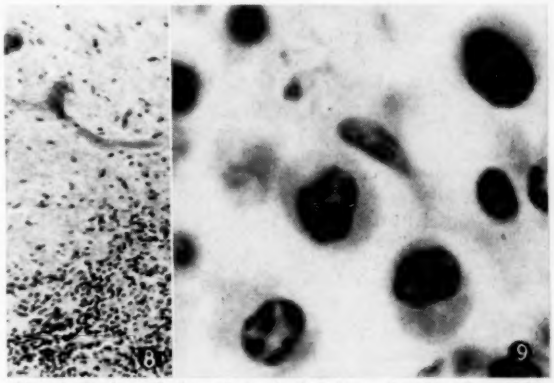

Fig. 8. Section of the spleen showing large deposits of amyloid (haematoxylin and eosin × 120).
Fig. 9. Myeloma cells in a section of bone marrow (haematoxylin and eosin × 1900).

of multiple myeloma (marrow) and Hodgkin's disease (lymph nodes). The second patient had Hodgkin's disease for 10 years after which pathognomonic evidence of multiple myeloma was found. The presence of amyloid in this case is of interest. Amyloidosis may occur in tuberculosis as well as in Hodgkin's disease,[11] and its association with multiple myeloma is often mentioned, but in a review of 51 cases by Glenchur *et al.*[10] it was found in only 2 cases. An earlier study of 51 cases of myelomatosis by Meacham[12] showed only 1 case with amyloidosis.

SUMMARY

A case presenting the pathological features of multiple myelomatosis, Hodgkin's disease and reticulum-cell sar-

coma is described. The interrelationship between the various cell types of the reticulo-endothelial system is discussed and the literature dealing with tumours of the reticulo-endothelial system, exhibiting neoplastic proliferation of several cell types, is reviewed.

We should like to thank the Superintendent of Baragwanath Hospital and Dr. M. B. Schwartz for permission to use the case records and the Director of the South African Institute for Medical Research for facilities granted. Mr. M. Ulrich produced the photographs.

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GOVERNMENT COMMISSION OF ENQUIRY INTO THE HIGH COSTS OF MEDICAL SERVICES AND MEDICINES

The above Commission was appointed by the Honourable the Minister of Health, and an announcement to this effect was published in Government Notice No. 6349 of 15 January 1960.

At the meeting of the Federal Council held in Pretoria early in March, it was agreed that information be obtained from the various Branches and Groups of the Association and that it be correlated by the Secretaries of the Association for submission to the Commission.

The memoranda so received were examined by the Secretaries in June, and the Chairman of Council agreed that the Association's memorandum be prepared in general terms and that the details supplied by the Branches and Groups be also submitted to the Commission.

This was done and the Association's memorandum and 19 memoranda submitted by the Branches and Groups were handed to the Secretary of the Commission on 10 June.

It would seem that the procedure followed by the Commission is to examine the memoranda supplied to it, and, if considered necessary, a questionnaire is drawn up and supplied to the writer of a memorandum with the request that the additional information indicated in the questionnaire be provided.

It is clear that the Commission will be visiting the major centres of the Union to take verbal evidence, but it would seem that such verbal evidence will only be received from those who have submitted memoranda and who have been asked to supplement their evidence orally. We have requested that the authors of all the memoranda we have submitted be invited to give such oral evidence. We have been informed that it is unlikely that the Commission will undertake its tour before October.

When the time arrives, it is likely that Branches of the Association will be asked to amplify their individual memoranda verbally, but the main evidence on behalf of the profession will be provided by the Executive Committee of the Federal Council.

VIERDE AKADEMIESE JAARDAG VAN DIE KARL BREMER-HOSPITAAL EN DIE FAKULTEIT VAN GENEESKUNDE VAN DIE UNIVERSITEIT VAN STELLENBOSCH

Die jaarlikse akademiese jaardag sal op Donderdag en Vrydag 8 en 9 September gehou word in die Burgersentrum, Bellville, Kp. Die volgende is die voorlopige program:

REFERATE

Donderdag 8 September

2.00 nm. Opening: Prof. F. D. du T. van Zijl.
2.15 nm. Besering van veneuse endoteel deur gekonsentreerde dekstrose-oplossing: Dr. B. J. van R. Dreyer.
2.35 nm. Die gebruik van ‚liquoid venule' vir bloedkwekings: Dr. J. G. Steytler.
2.50 nm. Onverwagte moederdood in die verloskunde: Dr. H. J. H. Claassens.
3.10 nm. Teepouse.
3.35 nm. Die invloed van silikonsuur op 'n paar respiratoriese ensieme: Dr. F. M. Engelbrecht.
3.55 nm. Beenmurg-oorplantings: Dr. T. Heyl.
4.15 nm. Die bepaling van die serum proteïen-spektrum by die Bantoe met behulp van elektroforese: Prof. A. J. Brink en dr. P. D. R. van Heerden.
4.35 nm. Gevalbespreking — Hiperparatiroïdisme: Dr. J. J. Heydenrych.
4.55 nm. Duisend kinders: Drs. J. D. Snyman en A. B. Murray.
5.15 nm. Die Departement Chemiese Patologie se werksaamhede in die lig van outomasie: Dr. C. P. Retief.

Vrydag 9 September

8.30 vm. Filmvertoning: ‚Griseofulvin in the treatment of superficial fungus diseases': Dr. H. van der Meulen.
8.55 vm. *Salmonella stellenbosch* — 'n Nuwe serotipe: Dr. H. D. Brede.
9.05 vm. Studies oor respiratoriese spiere: Dr. H. P. Wassermann.
9.25 vm. Gewigdraende amputasies: Dr. A. W. B. Heywood.
9.45 vm. Karsinoom van die serviks gedurende swangerskap: Dr. J. S. Coetzee.
10.05 vm. Pleurale biopsies: Dr. A. M. de Kock.
10.25 vm. Teepouse.
11.00 vm. Behandeling van antepartum eklampsie met keisersnit: Dr. P. F. M. du Toit.
11.20 vm. Hialien membraansiekte: Prof. H. W. Weber.
11.40 vm. Afbinding van die pankreasbuis by radikale pankreaskopreseksie: Drs. B. J. van R. Dreyer en J. S. Marais.
12.00 nm. Die probleem van narkose by spinaalfusie: Dr. S. V. Potgieter.
12.20 nm. Voorlopige verslag oor ‚Dumping'-sindroom: Dr. J. J. Heydenrych.
12.40 nm. Middagete.
2.00 nm. Geneeskunde in Amerika: Prof. A. J. Brink.
2.20 nm. Vitamien A-bepalings in pasiënte met karsinoom van die esofagus: Dr. J. A. du Plessis.
2.40 nm. Mesenchiem-gewasse van die nier: Dr. S. S. Grové.
3.00 nm. Die segmentele geaardheid van die milt: Dr. B. J. van R. Dreyer.
3.20 nm. Teepouse.
3.50 nm. Die behandeling van kinders met chroniese asma: Dr. A. B. Murray.
4.10 nm. Probleme van moderne hospitaal-infeksies: Dr. H. D. Brede.
4.30 nm. Placenta praevia: Dr. J. J. de Wet.
4.50 nm. Verkiesing van nuwe komitee.

Daar sal wetenskaplike sowel as farmaseutiese uitstallings wees.

AMPTELIKE AANKONDIGINGS : OFFICIAL ANNOUNCEMENTS

MEDIESE VERENIGING VAN SUID-AFRIKA : MEDICAL ASSOCIATION OF SOUTH AFRICA

ALGEMENE JAARVERGADERING

Kennis geskied hiermee dat die Algemene Jaarvergadering van die Mediese Vereniging van Suid-Afrika gehou sal word op Woensdag 19 Oktober 1960, om 9.30 vm., in die Ontspanningsklub van die Union Steel Corporation, Vereeniging.

Agenda

1. Notule
2. Jaarverslae
3. Verkiesing van Ouditeure
4. Inleiding van President
5. Ander Besigheid.

Na afhandeling van dié werksaamhede, word die Vergadering verdaag en om 8.15 nm. op dieselfde plek hervat, wanneer die President sy Voorsittersrede sal lewer.

Mediese Huis
Kaapstad
22 Augustus 1960

A. H. Tonkin
Sekretaris

FEDERALE RAAD

Kennis geskied hiermee dat 'n vergadering van die Federale Raad gehou sal word in die Ontspanningsklub van die Union Steel Corporation, Vereeniging, op 19, 20 en 21 Oktober 1960, begin 10 vm.

Agenda

1. Kennisgewing wat die Vergadering belê
2. Volmagte
3. Goedkeuring van notule van vorige Vergadering
4. Sake wat uit die notule voortvloei
5. Verslag van die Uitvoerende Komitee
6. Finansiële verslag van die Erepenningmeester
7. Verslae van ander Komitees
8. Ander sake
9. Nuwe kennisgewings van voorstelle.

Mediese Huis
Kaapstad
22 Augustus 1960

A. H. Tonkin
Sekretaris

ANNUAL GENERAL MEETING

Notice is hereby given that the Annual General Meeting of the Medical Association of South Africa will be held in the Union Steel Corporation Recreation Club, Vereeniging, on Wednesday 19 October 1960, at 9.30 a.m.

Agenda

1. Minutes
2. Annual Report and Balance Sheet
3. Election of Auditors
4. Induction of President
5. Other Business.

At the conclusion of business, the meeting will be adjourned and reconvened at 8.15 p.m. at the same place, where the President will deliver his Presidential Address.

Medical House
Cape Town
22 August 1960

A. H. Tonkin
Secretary

FEDERAL COUNCIL

Notice is hereby given that a meeting of the Federal Council will be held in the Union Steel Corporation Recreation Club, Vereeniging, on 19, 20 and 21 October 1960, commencing at 10 a.m.

Agenda

1. Notice convening the Meeting
2. Proxies
3. Confirmation of minutes of previous Meeting
4. Matters arising out of the minutes
5. Report of the Executive Committee
6. Financial statement by Honorary Treasurer
7. Reports of other Committees
8. Other business
9. New notices of motion.

Medical House
Cape Town
22 August 1960

A. H. Tonkin
Secretary

IN DIE VERBYGAAN : PASSING EVENTS

Dr. H. B. W. Greig, Head of the Department of Haematology, South African Institute for Medical Research, Johannesburg, has been invited to be the opening speaker in the section on 'experimental studies' at a Conference on Thrombolytic Activity and Allied Phenomena, which will be held on 18 - 21 September at Princeton, N.J., under the auspices of the National Heart Institute of the USA and the International Committee on the Nomenclature of Blood-clotting Factors. Dr. Greig will also attend the Eighth Congress of the International Society of Haematology in Tokyo on 4 - 10 September where he will present a paper on 'The isolation of material with pro-activator activity from human serum'. Dr. Greig has been awarded an S. L. Sive Memorial Travelling Fellowship to enable him to attend the Haematology Congress.

* * *

Dr. A. Zoutendyk, Head of the Blood Transfusion Service and Department of Immunohaematology, will officially represent the South African Institute for Medical Research at the Eighth Congress of the International Society of Blood Transfusion in Tokyo on 12 - 14 September, where he will read a paper on 'Rh factors C and G in South African Bantu'. Dr. Zoutendyk will also attend the Eighth Congress of the International Society of Haematology which is being held in Tokyo on 4 - 10 September.

* * *

Dr. W. M. Politzer, Head of the Biochemistry Department, South African Institute for Medical Research, Johannesburg, will attend the Fifth International Congress on Nutrition in Washington D.C. on 1 - 7 September 1960. He will read a paper on 'The incidence of diabetes mellitus in the Bantu of Basutoland' at the Congress.

Mr. H. Kramer has commenced practice as an obstetrician and gynaecologist at 902 Medical Arts Building, Jeppe Street, Johannesburg (telephone 23-1888/9). For the past 10 years Mr. Kramer has been doing postgraduate work in the UK at centres in London, Liverpool, Manchester, and Edinburgh as well as in the USA.

Dr. H. Kramer het as verloskundige en ginekoloog begin praktiseer te Medical Arts-gebou 902, Jeppestraat, Johannesburg (telefoon 23-1888/9). Gedurende die afgelope 10 jaar het dr. Kramer nagraadse werk onderneem in die V.K. in sentrums in Londen, Liverpool, Manchester, en Edinburg sowel as in die V.S.A.

* * *

Research Forum, University of Cape Town. The next meeting of Research Forum will be held on Wednesday 7 September at 12 noon in the Bennie de Wet Lecture Theatre, A-floor, Groote Schuur Hospital, Observatory, Cape. Dr. A. O. Lurie will speak on 'Adrenal function in malnutrition: (Part 2) kwashiorkor, and (part 3) aldosteronuria and the oedema of kwashiorkor' (by Drs. A. O. Lurie and W. P. U. Jackson). All interested are invited to attend this meeting.

* * *

Mr. Paul Marchand, M.D., Ch.M., F.R.C.S., thoracic surgeon, has recently returned from the USA and has resumed practice at 10 Clarendon Centre, Park Lane, Johannesburg. Mr. Marchand held a Wellcome Travelling Fellowship and undertook the study of open-heart and other cardiovascular surgery in the USA.

* * *

Dr. H. Hirsch, of Durban, has left the Union for London, where he intends doing postgradute study.

Association of Surgeons of South Africa (M.A.S.A.), Pretoria Sub-Group. The next meeting of this Sub-Group will be held on Friday 23 September at 5 p.m. in the Upper Lecture Theatre, Clinical Buildings, Pretoria. Mr. C. A. R. Schulenburg will report on the proceedings at the Second Biennial Congress of the Association of Surgeons which will be held in Durban on 17 - 20 September.

* * *

University of Cape Town and Association of Surgeons of South Africa (M.A.S.A.), Joint Lectures. The next lecture in this series will be held on Wednesday 7 September at 5.30 p.m. in the E-floor Lecture Theatre, Groote Schuur Hospital, Observatory, Cape. Mr. R. de Villiers will speak on 'The aortic valve with special reference to the surgical correction of aortic insufficiency'. All members of the Medical Association are welcome to attend this lecture.

* * *

South African Institute for Medical Research, Johannesburg, Staff Scientific Meeting. The next meeting will be held on Monday 12 September at 5.10 p.m. in the Institute Lecture Theatre. Dr. J. S. Harington, of the Nneumoconiosis Research Unit, will speak on 'Studies on silica shock in experimental animals'.

* * *

Society for Clinical and Experimental Hypnosis of South Africa (Southern Section). The Annual General Meeting of this Society will be held on Thursday 15 September at 8.15 p.m. in the E-floor Lecture Theatre, Groote Schuur Hospital, Observatory, Cape. The Chairman and the Hon. Treasurer will deliver their annual reports and new office bearers will be elected. The reports will be followed by a talk by Dr. J. G. Taylor on 'A behaviourist interpretation of hypnosis'. The telephone number of the venue is 55-1111.

* * *

Mr. C. D. Kisner, urologist, of 502 Medical Arts Building, Johannesburg, has changed his telephone number from 23-8200 to 23-8951.

Dr. C. D. Kisner, uroloog, van Medical Arts-gebou 502, Johannesburg, het sy telefoonnommer verander van 23-8200 na 23-8951.

* * *

Dr. Basil Bloch, M.B., Ch.B., M.Med. (O. & G.) (Cape Town), M.R.C.O.G., formerly registrar at Groote Schuur Hospital, Observatory, Cape, and King's College Hospital, London, has returned to the Union after spending 18 months in the UK and has now commenced practice as an obstetrician and gynaecologist at 401 Oasim, Pearson Street, Port Elizabeth. Telephone: Rooms 28030, if no reply 21545.

Dr. Basil Bloch, M.B., Ch.B., M.Med. (O. & G.) (Kaapstad), M.R.C.O.G., voorheen registrateur te Groote Schuur-hospitaal, Observatory, Kaap, en King's College-hospitaal, Londen, het nou na die Unie teruggekeer na 18 maande in die V.K. en het begin praktiseer as ginekoloog en verloskundige te Oasim 401, Pearsonstraat, Port Elizabeth. Telefone: Spreekkamer 28030, indien geen antwoord 21545.

BRIEWERUBRIEK : CORRESPONDENCE

PERSONAL DATA TO BE CARRIED IN CASE OF EMERGENCY

To the Editor: Presumably it may happen in casualty or other emergency situations that doctors may have to make rapid decisions about treatment of unconscious patients or in cases where they have no means of obtaining highly desirable data regarding the patient's medical history. A wrong decision in such cases may mean the loss of a life; prompt and correct action may be lifesaving.

It seems to me that doctors would be greatly assisted in all such cases if the person requiring attention carried on himself information which would include: (1) his blood group; (2) his allergies, if any, to such drugs as penicillin or antitetanus serum, or to anaesthetics; (3) any previous serious operations such as the removal of a kidney; (4) whether he is a diabetic (taking insulin or not) or an epileptic; and (5) whether he has had a course of tetanus toxoid injections.

Decisions would have to be taken on how this information should be carried and how to set up a system of internationally recognized symbols, identifiable by doctors anywhere in the world.

It is possible that everyone could carry a card with this information (what about our identity cards?) or, better still, that suitable symbols could be tattooed on the skin.

I realize that a large amount of work is required to implement my suggestion, but I am prepared to believe that in the Union of South Africa a dozen retired medical men could be found who would be willing to share the work. A start could be made with deciding what information is essential, with drawing up a list of symbols and with communicating with medical centres in other countries.

It would, no doubt, get the Union — and all other countries — off to a good start if the Government gave this enterprise its blessing, and possibly a modicum of financial support.

I should be happy if my suggestions bear fruit in 3, 5, 10 or even 25 years. The credit must go to whatever medical council or association takes the initiative and sees the scheme through.

30 Saxon Avenue — Albert M. Jacobs
Sandhurst — *Former Chairman, Escom*
Johannesburg
26 July 1960

IDENTIFICATION OF 'PENICILLIN-SENSITIVE' PATIENTS

To the Editor: I am prompted to write this letter by an occurrence in our outpatients' department recently, when a patient suffered very severe reaction after an injection of penicillin. Only then did he vouchsafe the information that he had reacted similarly after an injection in Lourenço Marques.

These reactions to penicillin are now occurring with such frequency that it seems to me that throughout South Africa there should be some means of identification for 'penicillin-sensitive' patients: a means that would offer protection — even if the patient were brought into hospital unconscious. Such a means of identification regarding 'pencillin-sensitive' persons would have to be something which presumably would be worn as a wrist band or just below the elbow, which would be recognized in any major hospital or clinic in the Union. It would have to be something which was uniformly worn, and ordered throughout the Union to be worn for the same type of reaction.

I write this letter to you with the thought that you will either give it publicity, or alternatively suggest some authority to whom the letter can be addressed.

McCord Zulu Hospital — Alan B. Taylor
28 McCord Road — *Medical Superintendent*
Durban
10 August 1960

[See Editorial comment on p. 753 — Editor.]

INCOME LIMITS FOR MEDICAL AID SOCIETIES

To the Editor: In his letter published in the *Journal* of 6 August, Dr. N. H. Pooler[1] states that he 'and many . . . fellow general practitioners are . . . most unhappy about the general trend of medical aid work'.

I should like to reply to some of the objections which he has raised:

Rules Governing Income Limits

The rules governing the income limits for members of medical aid societies have been formulated and amended over a number of years and accepted by Federal Council. I do not think we should find fault with individual words or phrases — such as 'gross income' — as long as we know what these are intended to convey. Perhaps a better term than 'gross income' would be 'total net income' — but all that this means is that a member should declare other sources of income in addition to his salary. It is possible that some members avoid supplying such figures to their medical aid societies — but the number of such members must be exceedingly small among the total of approximately 300,000 members and dependents belonging to medical aid societies. It is impossible, even for Federal Council, to legislate for any and every small infringement of the rules.

Dr. Pooler has 'never met nor heard of a medical aid society member whose benefits have been terminated because of his financial position'. This situation requires clarification. It is quite true that the medical aid society rules, as amended in recent years, limit the number of members earning more that £1,750 *per annum* to 3% of the total membership and makes provision for the payment of private fees by medical aid society members earning over £2,500 *per annum*.

Perhaps Dr. Pooler's difficulty in reference to the high income group can be explained on the basis that most of the older medical aid societies were recognized without these limiting clauses regarding income, but purely on the *average income* limit of all members which has been increased over the past 10 years from £700 to £1,100 *per annum* by Federal Council. The older medical aid societies maintain that any change in rules affecting them should be a mutual and not a unilateral decision. It is, therefore, held that the new rules relating to income groups should apply only to those medical aid societies who have applied for recognition since the introduction of the new rules. This may explain why no member in the higher income group has had his 'benefits terminated because of his financial position'.

The most recent official figures relating to medical aid societies are as follows (as at 1 September 1959):

Number of medical aid societies	126
Number of members	128,600
Number of dependants	185,196
Percentage of members earning over £2,500 *per annum*	0·8%
Percentage of members earning under £750 *per annum*	75%

It has been pointed out that executive members earning the higher incomes are a considerable asset to all concerned because they have access to the employers to subsidize funds. It must be remembered that many of these societies would not be able to exist without subsidy from their employers. Their administrative expense is approximately 9% of their total income, and in spite of this, with few exceptions, many of the societies plead that they have no reserve funds and, in fact, many say they are 'in the red'.

Negotiations have been proceeding between the Advisory Council of Medical Aid Societies and Federal Council with reference to this issue. It may be said that although no finality has as yet been reached, considerable sympathy was expressed in Federal Council with the medical aid societies' point of view, viz. that they were recognized before the new rules were made by Federal Council, that they were not consulted in the matter, and that no medical aid society infringes the *average income limit* clause.

General Practitioner's Consulting Fee of 12s. 6d.

Private consultation fees are not arranged on the basis of a preferential tariff which is a concession granted to medical aid societies by the Medical Association. It has often been said that private fees are unrelated to medical aid fees. Two points should be made: (1) that the private consultation fee for most general practitioners for the middle and lower income groups is in many instances not much more than the medical aid fee, and (2) that negotiations with medical aid societies have recently been initiated for an increase in general practitioners' fees.

Item 5 of the General Preamble to the Tariff. I think it is quite true that many medical aid societies fail to list 'those benefits excluded, or any limitations imposed by the Society' on patients' membership cards. The rare occasions that the card is inspected by doctors (or receptionists) would indicate that the few limitations are well known to most doctors and are included in Item 2 of the Preamble. This does not cause any real difficulty. I think it is a very minor fault.

Wealthy members of group schemes who choose to pay private fees. These patients, who are probably very few, do so voluntarily. Again the rules of a society apply to all members, otherwise difficulties could result from private contracts between members and doctors. If a 'wealthy member' is faced with heavy medical expenditure for major and prolonged illness, he may still resort to the privileges applicable to medical aid society members. Item 7 of the General Preamble may apply to these patients.

Overdue accounts. See the last paragraph of Item 2 of the General Preamble to the Tariff.

Item 7 of the General Preamble. This requires medical practitioners not to differentiate 'between which members of a medical aid society they will treat at tariff rates and which they will treat at private rates'. The contract made by the Medical Association with the medical aid society is for a tariff of fees which applies to *all* the members of a society which conforms to the Medical Association's requirements for recognition. It would include a large percentage of the lower-income groups who would otherwise be entitled to free hospital services for major illnesses. It would, therefore, seem unfair to expect a higher fee from those few members of a medical aid society who earn the higher salaries. On balance, I am sure the doctor benefits considerably by this arrangement. I cannot follow Dr. Pooler's contention that the Association is acting as a 'trade union' in this matter, nor do I think the words 'most vicious' are necessary. I am also very doubtful whether it is correct to accept 'wealthy' or other patients belonging to a medical aid society as private patients — even though they generously declare they will 'pay private fees rather than to let their doctor suffer from the fact that they have recently been forced to join such schemes'. I would point out that as one of the rules applicable to medical aid societies includes the phrase 'as the Medical Association cannot bind its members to this agreed tariff . . . ' it is competent for any doctor to operate outside the medical aid tariff, but for all members of a society.

I think Dr. Pooler may, perhaps, be considering medical aid societies and insurance companies as similar bodies. They are two very different types of organizations. Insurance societies, unlike medical aid societies, are bound to include a much higher percentage of insured in the higher-income brackets. It appears likely that the changing pattern of medical practice throughout the world, depending on major advances in medical science and economic factors beyond our control, will have its impact on South African medical practice in the near future. Federal Council has, I think, on the whole moved with the times and will no doubt face up to the problems of the future.

The medical aid societies have been built up on the basis of fairness and mutual cooperation. There are many doctors who would prefer to see the system of medical aid practice as it exists today continue, rather than have it replaced by highly commercialized institutions which have recently made devious inroads into our profession, or by a nationalized medical service. I am sure Dr. Pooler will agree when I say we should maintain good relations with medical aid societies and encourage their development.

404 Medical Centre A. L. Agranat
Jeppe Street
Johannesburg
17 August 1960

1. Correspondence (1960): S. Afr. Med. J., **34**, 680.

RADIOLOGICAL MEDICAL AID FEES

To the Editor: The Tariff of Fees for Approved Medical Aid Societies, while giving a fairly reasonable average fee, makes no provision for difficult examinations in radiology which require extra production costs and time.

A particular and frequent example is the radiological examination of the lumbar spine. The old, and bad, way of doing recumbent, AP and lateral views, is seldom done. A full set of films consists of AP and lateral views, 2 oblique views, an erect lateral view, and flexion and extension views with a lumbosacral angle — 7 views. The normal time to do a full radiological examination on a moderately difficult, fat patient, who wobbles a bit during the flexion and extension views, is an hour. With the repeats necessary and with average luck, it means that 9 films have to be done: it can easily be 11 films. The tariff fee of £3 13s. 6d. is absolutely ridiculous under these circumstances, for the production cost is more than this. The fee should be at least £5 5s. 0d. When it is remembered that a large number of cases in Government employment receive a reduction of 10% on the already low medical aid tariff, it seems that we should wake up to reality quickly!

I would suggest that the present fees should be the minimum for this work and that 50% surcharge be permissible in difficult cases.

Of all the professions it is certain that only the medical profession would put up with this state of affairs, where fees in certain cases do not cover production costs.

C. J. B. Muller

206 Dumbarton House
Church Street
Cape Town
16 August 1960

SOUTH AFRICAN SOCIETY OF PATHOLOGISTS

To the Editor: At a meeting held in Bloemfontein on 6 August 1960, a South African Society of Pathologists was formed. The objects of the Society are to advance pathology and to facilitate contact between those interested in pathology and related subjects.

Applications for membership of the Society are invited from suitably qualified persons engaged in research or in the teaching or practice of pathology or any allied science. Persons joining the Society before the end of the current year will be founder members.

Applications for membership should be submitted to the undersigned.

J. Metz
Hon. Secretary-Treasurer

South African Society of Pathologists
P.O. Box 1038
Johannesburg
17 August 1960

ILLEGIBLE SIGNATURES

To the Editor: We have recently been receiving numerous complaints from chemists, medical aid societies and the Registrar of Births and Deaths regarding the illegibility of doctors' signatures on documents.

The Branch Council feels that it is advisable to bring this to the notice of all medical men in South Africa, and has suggested that doctors be advised to print their names in block letters above their signatures on prescriptions, certificates, etc. This could possibly be effected with a rubber stamp.

J. Schwartz
Administrative Officer

Southern Transvaal Branch
Medical Association of South Africa
P.O. Box 10102
Johannesburg
17 August 1960

THE PERSONAL DOCTOR

To the Editor: As a result of Professor J. F. Brock's stimulating letter[1] of 1 July on the subject of 'the personal doctor', the Cape of Good Hope Faculty of the College of General Practitioners elected a committee, consisting of the undermentioned practitioners, to investigate the subject and to give some reply.

Our committee studied much material available on the subject and, after not a few hours of discussion, we have reached some conclusions. Although these conclusions were arrived at unanimously we should like to make two points: Firstly, some of us have further ideas which were not unanimously supported and will not therefore be produced at this stage; secondly, the views expressed here are the views of this committee only and in no way are they the special views of the Cape of Good Hope Faculty or of the College of General Practitioners.

Professor Brock is well known for his wide perspectives in medicine, but we feel in this instance that he has not seen the full implications of the problem of the need for 'the personal doctor'. We feel that it is not the status of the general practitioner which is at stake but rather the status of medicine itself as being one of the three traditionally learned professions of theology, law and medicine. These learned professions originated, in the primitive community, from the witch-doctor who was priest, law-giver and medicine man. His descendants have traditionally been the men of standing in any community. Today, with the development of the scientific attitude and the advances in technology, doctors have at their disposal wonderful and complicated chemicals, machines, and materials which have led to highly technical procedures. This has led to the growth of specialism in a high degree. The doctor is becoming more and more a technologist and less and less a member of a learned profession. Concomitantly society has become more highly organized, but the patient, just as always, needs his 'guide, philosopher, and friend'. Why coin another phrase 'the personal doctor'? 'A rose by any other name . . . '. Society needs the general practitioner. Society needs the man with the broader view now, more than ever before.

We do not hold with the view so often expressed by the technocrats of medicine that 'the whole field of medicine today is too vast to be adequately comprehended by one man'. If neurosurgery, cardiovascular surgery, much of urology, cardiac catheterization, liver biopsy, and other such refinements which would never be in the province of the general practitioners' work are excluded, then any competent intellect could, and does, cope with the demands.

We do not agree with the definition of a general practitioner, given by Dr. Fox, who must 'provide full medical and surgical care and he would lose face if he proved less than omnicompetent'.

We strongly support the definition of a general practitioner given by our colleague Dr. Hunt: 'a doctor in direct touch with patients, who accepts continuing responsibility for providing or arranging their general medical care, which includes the prevention and treatment of any illness or injury affecting the mind or any part of the body'.

Not, sir, a man who strives for omnicompetence, but a man who at once is competent but aware of his limitations.

We are disturbed at the possible implications of the training of 'the basic doctor' if this should imply any lowering of the standard of undergraduate medical education. We strongly urge the maintenance of the highest academic standard of the undergraduate. We oppose any skimping of basic disciplines.

We suggest that Professor Brock's indefinable 'something else' is a perspective that might ideally be given to the undergraduate by the general practitioner. Perhaps the general practitioner could aid the teachers in the medical schools, who are all specialists, by imparting a touch of holism in medicine. Could the general practitioner become the catalyst in the process of undergraduate education which would show the success of the time-proven patient — general practitioner — consultant relationship?

We therefore unanimously recommend:

1. The establishment of a coordinating body to represent the common interests of the College of General Practitioners and the universities.
2. That departments of general practice be established in medical schools so that general practitioners could teach the undergraduate student in out-patients' departments, wards, and in their own general practices.
3. That the general practitioner should be an integral part of the hospital team.
4. That general practitioners should participate in ward rounds with specialists and students.
5. That a period of active general practice is essential in the training of a specialist and that the South African Medical and Dental Council should reinstate this concept in its regulations.

In conclusion we should like to thank Professor Brock for his timely introduction of a subject of such great importance to all of us who are members of this learned profession of medicine.

F. E. Hofmeyr
J. D. de B. Joubert
B. J. Kaplan
P. F. Oates
A. G. Paterson
P. A. Rens
S. Schur
D. Turner
H. R. B. Wilson

Cape Town
20 August 1960

1. Correspondence (1960) S. Afr. Med. J., 34, 640 (23 July).